Atrial Fibrillation and Cognitive Impairment

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Abstract

Background

In our aging population the burden of dementia is increasing, necessitating the urgent identification of treatable risk factors. Small cross-sectional studies demonstrate associations between non-valvular atrial fibrillation (NVAF), silent cerebral infarction and decreased cognitive function, but there are few longitudinal studies in this area. This thesis reports the results of a prospective longitudinal cohort study of cognitive decline in people with recent-onset NVAF compared to controls.

To inform the thesis, an extensive literature review was undertaken . This included searches on NVAF and cognitive decline, NVAF and silent infarction, epidemiology of NVAF, other risk factors for cognitive decline, epidemiology of cognitive decline and the neuropsychological tests included in the CAFE battery.

Methods

362 people over 60, screened in primary care, underwent baseline assessment including a battery of neuropsychological tests, repeated at 12 months (n=304). Cases (n=175) with recent-onset NVAF, were matched for age, sex and GP practice with controls in sinus rhythm. Data were compared using SPSS software (version 11) with both parametric and non-parametric analysis.

Results

Baseline characteristics, including cognitive function, were similar for cases and controls. There was wide variation between individuals in change in performance on the neuropsychological tests

over 12 months, with some improving and some deteriorating for each sub-test. Cases (NVAF) significantly ($p<0.05$) deteriorated in four subtests measuring attention/ non-verbal memory, and significantly ($p<0.05$) improved in two subtests measuring verbal memory. Controls significantly ($p<0.05$) deteriorated and improved in the same sub-tests as cases, but significantly ($p<0.05$) deteriorated in another three subtests measuring attention/non-verbal memory, and significantly ($p<0.05$) improved in another six subtests. Treatment with warfarin or aspirin did not appear to be associated with change in cognitive status.

Conclusions

At baseline there was no significant difference in cognitive function between cases in NVAF and controls in sinus rhythm. At follow-up there was no consistent relationship between NVAF and cognitive decline over 12 months, nor any apparent effect of antithrombotic therapy. Explanations include true independence of NVAF and cognitive decline, or too short a follow-up period. An additional follow-up at 36 months is underway to explore this further.

Notes on contributors to the thesis

This thesis contains my own, original work.

I have received advice from my supervisors and others in study team.

In a minor part of the background section of this thesis (chapter 3), I have included part of a literature review for my MSc thesis (June 2001), in order to inform the knowledge base for my MD research. In addition to this literature review, I carried out extensive separate literature reviews solely for the MD. I discussed the inclusion of the small section from the MSc with assessors and supervisors throughout the study period, and it was felt to be appropriate and useful to include this.

What I was responsible for in the study

I made a major contribution towards the study design, obtained funding for the study (through the fellowship scheme), obtained ethical approval for the study, set up the study, designed patient and GP letters and information leaflets, approached general practices, screened all GP notes and identified all potential participants, visited all patients at baseline, carried out all physical examinations, carried out more than half of all patient interviews at baseline and approximately half at follow-up, analysed all data (with assistance from the project statistician) and interpreted this (with support from my supervisors).

How I benefited from undertaking this study

Carrying out the work reported in this thesis enabled me to acquire highly valuable research skills including: literature searching, critical appraisal, organisational skills, time management, experience in the practicalities of undertaking a piece of research and report writing. In addition I have broadened my understanding of a specific area, allowing the development of expertise. Other more transferable skills gained include experience in writing grant applications and applications to ethics committees, appreciation of the limitations of others' research and numerous skills gained through the experience of undertaking a well-structured project supervised by experienced researchers.

Chapter1- Introduction

More than half a million people in England and Wales currently fulfil diagnostic criteria for dementia.[1] As the population ages, progressive cognitive decline leading to dementia will become even more prevalent, placing an additional burden on patients, their carers, and the NHS. It is therefore imperative that risk factors for dementia are identified and treated in order to prevent dementia or slow cognitive decline wherever possible.

Published work has demonstrated that cardiovascular risk factors may predispose not only to vascular dementia, but may also contribute to a dementing process similar to Alzheimer's disease.[2] This may be explained by pathological mechanisms,[3,4] clinical effects and/or common risk factors[5] for both vascular and Alzheimer-type dementia. Consequently, there is potential for prevention; for example it has been suggested that anti-platelet therapy in hypertension may be associated with reduced risk of dementia.[6]

Mild cognitive impairment has been shown to precede more than half of cases of vascular dementia,[7] and half of those with vascular cognitive impairment (i.e. cognitive impairment of vascular origin) without dementia have been shown to develop dementia within 5 years.[8] Identification of such 'at-risk' groups, for example those with NVAF, offers potential for preventive measures.

Non-valvular atrial fibrillation (NVAF), present in 5% of the over 65's,[9] is an established independent risk factor for stroke and a potential contributor to cognitive decline and vascular dementia through silent cerebral infarction.[10-13] NVAF could therefore be a modifiable risk factor for dementia and cognitive decline of both Alzheimer's and vascular aetiologies. To date research addressing an association between atrial fibrillation and cognitive status has been primarily restricted to small cross-sectional studies of selective populations with neither

careful consideration of potential confounders nor of the effect of antiplatelet or anticoagulant therapy. Because cross-sectional studies measure exposure and disease outcome simultaneously, they cannot establish aetiology or causation.[14] However, they are useful in generating aetiological hypotheses and a number of cross-sectional studies addressing NVAF and cognitive decline, including our pilot study in the North of England,[15] have demonstrated that those with atrial fibrillation have significantly lower scores on neuropsychological testing than those in sinus rhythm.[16-20] Only one study in this area has demonstrated lack of association between NVAF and atrial fibrillation. [21]

Primary and secondary stroke prevention studies in NVAF have demonstrated reduction of stroke risk through use of antithrombotic therapy. However, literature in the last five years suggests that the uptake of such treatment into clinical practice has been variable. This may be in part because of the difficulties in weighing up the risks and benefits of therapy.[22,23] Clarification of the potential role of antithrombotic agents in reducing the risk of cognitive decline in patients with NVAF in addition to stroke risk reduction would help to inform the clinical decision making process when faced with a patient for whom such therapy is being considered.

This prospective cohort study aimed to explore whether or not older people with NVAF have an increased risk of cognitive decline over time when compared with controls in sinus rhythm. This builds upon a pilot study and the limited existing work in this field. The ideal study design to assess the effect of antithrombotic therapy on cognitive status would be a randomised controlled trial. However, this would be unethical since the protective effect of warfarin and aspirin against stroke is well proven.[24] This therefore suggests that a more appropriate study design to explore such an association would be a prospective inception cohort study of a representative population, with repeated assessment of cognitive function

and analysis of the potential impact of treatment with antithrombotic therapy. [25] The Cognition and Atrial Fibrillation Evaluation (CAFÉ study) is such a study, with a cohort as close to inception as was feasible (recruiting only those with a diagnosis of NVAF in the last 5 years). In this thesis, CAFE's findings are reported.

Aims and objectives: The aim of the CAFE study was to determine whether NVAF confers additional risk for the subsequent development of cognitive impairment or cognitive decline. The objectives were to determine:1) whether NVAF in the community is associated with poorer performance on detailed neuropsychological testing than matched controls in sinus rhythm; and 2) whether cognitive function declines more over time in NVAF cases than in matched controls.

Hypotheses: The null hypotheses tested in this study were as follows: 1) the cognitive function of people with NVAF is no different to that of age and sex-matched controls in sinus rhythm, when assessed by detailed neuropsychological testing; and 2) the decline in cognitive function over time in people with NVAF is no different to that of controls. Secondary null hypotheses included: 1) the cognitive function of cases with greater risk of stroke is no different to that of cases with lesser risk of stroke; and 2) the decline in cognitive function over time in cases with greater risk of stroke is no different to that of cases with lesser risk of stroke.

CAFÉ was a community-based, prospective, longitudinal cohort study (N= 362), with follow-up at one year. The study compared the performance on detailed neuropsychological testing of participants with atrial fibrillation with that of matched controls in sinus rhythm. In addition, cases were stratified according to treatment with aspirin or warfarin. Results were

also stratified according to stroke risk (due to cerebrovascular risk factors) for cases only.

CAFE's baseline results represent the largest cross-sectional analysis comparing cognitive function in older people with NVAF or sinus rhythm, adding considerably to previous cross-sectional data. The results of CAFE's 12-month follow-up represent the only substantial longitudinal study of cognitive function in those with NVAF reported to date. As such the findings are of considerable interest and have implications for future research into a potentially preventable cause of dementia.

Definitions of terms used in the thesis

Atrial fibrillation: A common cardiac arrhythmia resulting in a continuous, rapid activation of the atria, with electrical response of the atria but conduction of only a proportion of the electrical activity and very little mechanical response of the atria. Non-valvular atrial fibrillation (NVAF) is atrial fibrillation in the absence of valvular heart disease.

Cognitive impairment: When calculating the sample size for this study, cognitive impairment was defined as a (negative) difference in score of 10% on a basket of tests. When interpreting the results of the study, all differences (even those below 10%) were reported. This was to enable to reader to understand all changes present in the sample. Any difference in scores of 10% or greater would have been highlighted had they occurred.

Types of cognitive impairment: different methods exist for grouping different types of cognitive impairment, but commonly used definitions are: -

Cognitive impairment, no dementia (CIND) describes those who have demonstrable cognitive impairment, with low MMSE score, which does not fulfil criteria for dementia.

Age-associated memory impairment (AAMI) is defined as memory test performance of at least one SD below the mean observed for young adults. In *Age-associated cognitive impairment (AACI)* performance is at least 1.5 SD below the mean observed on any test of cognitive function.

Mild cognitive impairment (MCI) is defined as a transitional stage between normal ageing and dementia, with demonstrable cognitive impairment where criteria for dementia are unmet.

Types of dementia: Dementia is defined as a global impairment of memory, thinking, intellect and personality, without impairment of consciousness. Vascular dementia includes

all dementias due to vascular causes (discussed further in Chapter 3), for example multi-infarct dementia, strategic-infarct dementia, subcortical ischaemic vascular dementia, hypoperfusion dementia, haemorrhagic dementia and dementias caused by specific arteriopathies. Other types of dementia are less relevant to this thesis, but include Alzheimer's disease (AD), dementia with Lewy bodies and mixed AD and vascular dementia.

Biological plausibility of the hypothesis:

The pathophysiological explanation underlying this study's hypothesis is that NVAF leads to uncoordinated and inadequate contraction of the atria such that there is incomplete ventricular filling, pulmonary venous congestion and decreased cardiac output. The uncoordinated contraction of the atria increases the risk of formation of micro-emboli, which in turn can obstruct cerebral arterioles leading to multiple silent cerebral infarctions. Over time the accumulation of many small silent cerebral infarctions in areas of the brain involved in cognition may lead to gradual onset of cognitive decline. An alternative explanation is that the decreased cardiac output resulting from NVAF leads to cerebral hypoperfusion, which in turn causes ischaemic damage to critical areas of the brain, resulting in cognitive decline.

Pilot study

A pilot study was undertaken in Gateshead, England in 1998, prior to the work reported in this thesis[15]. This involved comparison of 27 participants with NVAF with 54 age and sex matched controls in sinus rhythm. The cohort underwent the same battery of neuropsychological tests as used in the main study reported in this thesis, and NVAF was associated with poorer performance on all subtests of the neuropsychological test battery. The differences were significant for the delayed logical memory subtest (score of 38.7 for cases,

49.4 for controls, p=0.02), PASAT 4 (score of 41.9 for cases, 53.8 for controls, p=0.02) and PASAT-2 (score of 25.6 for cases, 34.7 for controls, p=0.08).

Chapter 2 – Risk factors for cognitive decline

- Part 1: Literature search methodology
    - Purpose of searches
    - Search strategy
    - Sources other than electronic database searches
    - Selection of abstracts and full texts
    - Study quality

- Part 2: Findings from the literature
    - a) Findings from the literature on atrial fibrillation as a risk factor for cognitive decline
    - b) Findings from the literature on the epidemiology of atrial fibrillation
    - c) Findings from the literature on other risk factors for cognitive decline

- Chapter 2 Summary

Part 1: Literature search methods

Purpose of Searches

Literature searches were undertaken prior to commencement of the study and at intervals throughout the project. The search on atrial fibrillation, silent cerebral infarction and cognitive decline (search one) informed study design and quality, reduced the likelihood of duplication and provided understanding of the issues specific to the study of atrial fibrillation and cognitive impairment and decline. The search on epidemiology of NVAF (search two) helped to ascertain the importance of addressing the research question and will also aid future incorporation of findings into practice through policy and strategic dissemination. The search on other risk factors for cognitive decline (search three) enabled identification of potential confounders. These could then be addressed in the study methods and analysis of results. A search for risk factors for stroke in atrial fibrillation was undertaken since this was consistent with the pathological mechanism in the study hypothesis, such that risk factors for stroke in atrial fibrillation may also be risk factors for silent cerebral infarction in atrial fibrillation.

Although background knowledge of studies of risk factors for stroke alone, with no focus on cognitive function was necessary, these studies were not systematically searched for. This was because although silent infarcts are part of the hypothetical pathway to cognitive decline in this study, I decided that for the purposes of this thesis it was more appropriate to concentrate on studies of cognitive function.

Search strategy (detailed strategies are in Appendix 1)

Choice of electronic database

Medline (searches 1,2 and 3), Embase (searches 1,2 and 3) and PsycINFO (searches 1 and 3) were the most appropriate databases for all of the searches outlined in this chapter since they are most likely to include journals publishing relevant articles. Medline was searched from 1966 to January 2001 and repeated on 2nd March 2004. Embase was searched in January 2001 and repeated on 2nd March 2004. PsycINFO (previously Psychlit) was searched from 1984 to January 2001.

Use of methodological filters and existing search strategies

i) For searches on studies of atrial fibrillation, silent cerebral infarction and cognitive decline (search 1)

The most appropriate study design to explore this topic would be longitudinal cohort studies with prospective follow-up of a representative community-based population.

The McMaster strategies[26,27] for identification of articles on prognosis and on aetiology, causation and harm[26,27] were appropriate for searching for longitudinal studies, our main area of interest.

The Cochrane Dementia and Cognitive Impairment Group (CDCIG)[28] is a working group of experts who regularly undertake and organise systematic reviews of trials on dementia and cognitive impairment. Although they are primarily concerned with randomised controlled trials, their search strategies are comprehensive, sensitive and up to date, and focus on cognitive decline and dementia. Their search strategy for detecting studies on cognitive impairment and dementia was modified for this study.

No published strategies exist for identification of articles on NVAF. Therefore, with permission, I used a validated strategy devised by another researcher[29,30]

The two McMaster strategies described above were combined with the core section on cognitive decline and dementia from the CDCIG and the NVAF strategy to create a detailed search strategy which could be applied to Medline, Embase and PsycINFO (see appendix).

The above search was suitable for retrieving longitudinal studies. However, much of the work in this field is cross-sectional in design, therefore in addition a more basic search was undertaken combining the NVAF search described above with the CDCIG strategy but without combination with the McMaster strategies.

ii) For searches on epidemiology of NVAF (search 2)

The aforementioned McMaster strategies for identification of articles on prognosis and on aetiology, causation and harm [26.27] were combined with the validated NVAF strategy, with the addition of search terms to include articles focusing on stroke risk for searches on risk factors for stroke in atrial fibrillation.

iii) For searches on other risk factors for cognitive decline (search 3)

The McMaster strategies described above were combined with the adapted CDCIG strategy. The ideal study design to explore risk factors for cognitive decline would be a community–based, prospective cohort design with sufficient follow-up. The search strategy was devised to include such studies. There were no further explicit inclusion criteria (for screening abstracts) for this search, other than that the studies addressed risk factors for cognitive decline. This differs from the more detailed and specific inclusion criteria for the search on epidemiology of cognitive decline (Chapter 3), which used the same search strategy.

iv) Specificity and sensitivity

Search 1 was designed to be highly sensitive, therefore with less specificity, to maximise the number of articles identified. For this search the priority was to ensure all pertinent articles were retrieved, since these studies were of immediate relevance to the CAFÉ study.

For searches 2 and 3, the aim was to broaden the knowledge base on the broader subject areas of relevance to CAFÉ. Since these searches covered wider topic areas the potential number of articles retrieved was huge; therefore the search strategies were designed to be specific rather than sensitive.

Sources other than electronic database search:

In addition to formal literature searches, other sources of information were used to inform this study. These sources included: -

Websites:

The evidence-based mental health website[31], a joint venture between the BPS (British Psychological Society), the BMA and the Royal College of Psychiatrists was searched, including an individual search of the journal " Evidence based mental health" via the website.

The Cochrane Library provided useful information, as described earlier, and the Medical Research Council website[32] provided a list of papers and conferences, published and in press, with abstracts.

Searches of other websites were unproductive.

Grey literature:

Contact with relevant experts in the field led to contact with further experts, who provided information on specific ongoing studies and also pointed out potential papers that may have been missed by the literature search. Such information was also provided by supervisors, colleagues and

contacts from conferences. In addition a number of papers were encountered through other opportunistic methods such as generally keeping up to date with the literature and attending conferences. The web-sites above and bibliographies of studies also provided a potential source of grey literature. In addition, the National Research Register[33] and Centrewatch[34] were used to search for ongoing studies.

Selection of abstracts and full texts

A protocol was developed to identify articles for which full text should be obtained. This was designed to include desired characteristics of relevant papers and was used when screening abstracts from the electronic database searches, in order to identify studies which could address the research question. The identification of abstracts from electronic databases was designed such that it would initially be maximally sensitive in order to minimise the possibility of overlooking relevant articles. The search strategies were then modified according to the number and relevance of abstracts retrieved, for example searches 2 and 3 were modified to become more specific, due to the huge number of research papers obtained in the initial searches.

Study quality

Variation in study quality may result in biased conclusions, since studies of differing quality will produce results of varying reliability. In addition the appropriateness of the study sample, design, and data collection characteristics may influence results.[35,36] Assessing quality of studies in this way made interpretation of their findings more accurate and also helped to inform the design and conduct of CAFÉ. Literature on the appraisal of epidemiological research suggests consideration of the following issues when appraising validity of epidemiological research: -

- **The study sample** should be well defined at the level of both invitation to participate and agreement to participate, and should be representative of the entire population from which they were recruited. Potential biases which need to be considered at this stage include selection bias, for example did those invited to participate differ from those not invited in important characteristics which may impact upon cognitive decline? In addition, what was the baseline risk of cognitive decline - at what point in the progression of cognitive decline were patients when they entered the study?
- **The period of follow-up** needs to be sufficiently long to allow outcomes to occur, and sufficiently complete to permit follow up of an adequate proportion of the cohort. The literature searches (searches 1 and 3) intended to explore the length of follow-up required to show significant cognitive decline and the likelihood of the outcome event (i.e. cognitive decline in those aged 60 years and over) in a specified time period (i.e. the follow-up period).
- **Loss to follow-up** would jeopardise a study's validity since we are looking at relatively low-risk conditions (AF and cognitive decline). In addition, this could lead to bias if occurrence of important characteristics differed between those who were and were not followed up.
- **Outcome criteria need to be objective and unbiased** Since there is no internationally recognised neuropsychological test battery in use, the outcome criteria for searches one and three vary. It is likely that studies which report the rate of cognitive decline using a recognised scoring system that has been validated and published elsewhere will be more valid. Another source of potential bias, observer bias, would be prevented if the observer measuring cognitive function is blinded to known likely risk factors for dementia, particularly the risk factor which is the focus of the study (e.g. for this study this would be NVAF).

Part 2: Findings from the literature

a) Findings from the literature on atrial fibrillation as a risk factor for cognitive decline

1. Evidence for an association between silent cerebral infarction and atrial fibrillation

One study of a cohort of patients with atrial fibrillation demonstrated that 23 of 72 asymptomatic patients with AF had MRI features of cortical infarcts.[37] Another prospective study noted evidence of cerebral infarction on MRI investigation of 14 out of 15 asymptomatic patients with AF.[38] This study also found that those patients on warfarin treatment developed fewer additional periventricular hyperintensities at 12-month follow-up than those not treated with warfarin. In both of these studies however, the numbers were very small and there was no control group. Another, larger cross-sectional study demonstrated a significantly increased risk (relative risk 2.2) of periventricular white matter lesions in those with atrial fibrillation compared to sinus rhythm controls, but no increased risk of subcortical white matter lesions.[39]

These findings for chronic NVAF contrast with other work describing no increased risk of silent cerebral infarcts in those with paroxysmal AF.[12]

Larger studies of those with AF who have already suffered clinical stroke include the following: Kempster et al[13] found that those with AF had three times the incidence of silent infarcts when compared to controls in sinus rhythm; and a small longitudinal study[37] described an increased likelihood of development of symptomatic brain infarction in patients with AF who had pre-existing silent cortical strokes when compared to those with AF who had no previous silent cortical strokes on MRI, suggesting that silent infarcts may predict symptomatic infarcts.

Studies of primary and secondary stroke prevention with warfarin and aspirin also address this issue. For example the SPAF primary prevention study included detection of silent, predominantly lacunar, infarcts in 37 of 141 patients with AF. [40] In the SPINAF study,[41] a primary prevention study of 516 patients with AF, 76 had evidence of silent infarct at entry into the study, associated with a history of hypertension, elevated mean systolic blood pressure or angina. A study of 985 AF patients with recent TIA or non-disabling stroke found that 139 had evidence of silent infarct on CT scan, with or without co-existing evidence of symptomatic infarcts. [42]

An autopsy study of 966 patients confirmed that those with a history of AF or hypertension had a greater number of silent cerebral infarcts than those without these conditions.[11]

2. Evidence for an association between atrial fibrillation and cognitive decline

A number of cross-sectional studies demonstrate that those with atrial fibrillation have significantly lower scores on neuropsychological testing than those in sinus rhythm: -

- Kilander et al found that men with NVAF had significantly ($p<0.01$) lower scores on MMSE and Trail-Making Tests than those in sinus rhythm, independent of history of stroke, diabetes, hypertension and poor left ventricular function.[20]
- Sabatini et al demonstrated significantly lower MMSE scores in those with NVAF compared to those in sinus rhythm.[17,19,20]
- A cross-sectional analysis of the longitudinal Rotterdam study demonstrated a statistically significant positive association between atrial fibrillation and both cognitive impairment (odds ratio 1.7) and incidence of dementia (odds ratio 2.3) of both vascular and Alzheimer-type aetiologies. This study used an extensive neuropsychological assessment for diagnosis of dementia, but only used the MMSE (<26) to diagnose cognitive impairment. [18]

Only one study in this field demonstrated lack of association between NVAF and cognitive impairment:-

- The InCHIANTI study reported that atrial fibrillation was statistically significantly (p=0.04) more prevalent in those with low cognitive performance with subcortical features than those with high cognitive performance or without subcortical features. However, this became non-significant (p=0.11) after adjustment for age, suggesting no significant association between NVAF and poor cognitive function. [21]

The only longitudinal study retrieved was a study of 411 patients undergoing coronary artery bypass grafting. This work reported more cognitive decline 6 weeks after surgery in those who developed post-operative atrial fibrillation (p=0.036). This study used the Randt Memory Test, Digit Span and Symbol subtests of WAIS, Wechsler Memory Scale Figural Memory test, Trail Making Test, and Rey Auditory-Verbal learning test. [16]

Though not focused solely on NVAF, a recent cross-sectional analysis of the Framingham Study cohort demonstrated that those with higher 10-year risk of stroke had poorer performance on neuropsychological testing. Although the study was not designed to look specifically at NVAF and the number of participants with NVAF was small (n= approximately 65), the presence of NVAF was found to be associated with poorer performance on tests of abstract reasoning and visual-spatial memory. The presence or absence of NVAF is a variable in the Framingham stroke risk calculation. [43]

Published work has demonstrated that vascular risk factors including NVAF may lead not only to vascular dementia, through silent cerebral infarcts, but also to a dementing process similar to Alzheimer's disease, in addition to 'mixed' aetiology dementias. [44] Post-mortem studies[4] have demonstrated that a high proportion of dementias have both vascular and Alzheimer-type

pathological changes. Suggested pathological mechanisms for this include a direct effect of vascular disease on the pathological process, for example cerebral ischaemia may lead to deposition of amyloid and may disturb the blood-brain barrier, and inflammation may also play a role.[44] Finally, there may be common risk factors for both vascular and Alzheimer-type dementia,[44] with potential for prevention; for example the Syst-Eur trial demonstrated less dementia in those who received anti-platelet therapy. [6,44]

3. Pilot Study

Prior to commencement of the work outlined in this thesis, a pilot study had been carried out. [15] This local, community-based cross-sectional study demonstrated that older people with NVAF and no history of stroke performed more poorly on detailed neuropsychological testing than did matched controls in sinus rhythm. The difference was most marked in the memory and new learning parts of the test. However, observation of change over time was not performed in the pilot, therefore it was not possible to determine whether cognition changed over time. This study generated the hypothesis for the work described in this thesis.

4. Evidence for the relationship between the duration of atrial fibrillation and the presence of silent infarcts or cognitive decline

Limited evidence is available on this subject. The work done by the EAFT study group[42] found no significant association between the duration of AF and the presence of silent infarcts. However, the study may not have accurately measured the exact time of onset of AF, a problem exacerbated by the often asymptomatic nature of AF.

b) Findings from literature on the epidemiology of atrial fibrillation

1. Prevalence and nature of AF, risk of stroke and the role of anticoagulants in prevention

Many studies in the UK and internationally have demonstrated that non-valvular atrial fibrillation (NVAF) is a common condition which increases with age. Estimates of prevalence range from 1 – 3% in those under 60 years to 9% in those over the age of 80 years,[45-49] although these studies are from different countries, and some are small, using selected populations. The incidence approximately doubles with each decade of adult life. Between 55 and 64 years the incidence is 2 to 3 new cases per 1000 population, rising to an incidence of 35 per 1000 population between the ages of 85 and 94 years. [50] A large, community-based prevalence study in the UK described an overall prevalence of 4.7% in the over 65's rising to 10% in men over 75 years. [9]

Most NVAF occurs in those with cardiovascular disease. [51] Cardiac failure, left ventricular hypertrophy and diabetes have been shown to be associated with NVAF.

Chronic AF is associated with doubling of overall mortality even when adjustments are made for pre-existing cardiovascular conditions with which AF is associated. [51,52] With ageing populations in the developed world, AF has become the most common arrhythmia diagnosed in hospital. [53] AF results in haemodynamic effects due to irregular ventricular filling, and increased risk of atrial thrombus formation. Symptoms range from palpitations to pulmonary oedema, with thrombus formation leading to cerebral infarcts and clinical stroke.

Management options to reduce these complications of NVAF include restoration of sinus rhythm, but this is often unsuccessful, short-lived or inappropriate. Management of established NVAF includes rate control (commonly digoxin) and anticoagulation or treatment with antiplatelet agents to prevent thrombus formation. A study comparing the two management options found that those assigned to rhythm control had no survival advantage over those assigned to rate-control. [54]

Randomised controlled trials have demonstrated the efficacy of anticoagulants in preventing the risk of stroke in patients with NVAF, [24,55-61] being more effective than aspirin; and the benefits of antiplatelet therapy have been further confirmed by recent meta-analyses. [24,62-64]

A large proportion of patients in the community would be likely to benefit from the use of antithrombotic therapy. [9,65] Appropriate use of anticoagulants is now well-known and widely accepted[66] and the importance of anticoagulation is reflected in the NHS National Service Framework for Older People, which includes a milestone for the identification and treatment of patients by 2004 at risk of stroke because of atrial fibrillation. [67] Nonetheless, many studies have revealed apparent under-use of warfarin. [9,68] The work described in this thesis may help to highlight the importance of appropriate identification and management of people with NVAF.

2. Findings from the literature on risk factors for cerebral infarction/ stroke in atrial fibrillation

Data from longitudinal analyses of study cohorts (control groups and/or aspirin treated trial participants with atrial fibrillation) has been used to identify potential risk factors for stroke.[69] Four such risk stratification schemes, specifically for those in atrial fibrillation, are the Stroke Prevention in Atrial Fibrillation (SPAF) scheme, the Atrial Fibrillation Investigators (AFI) schemes, the American College of Chest Physicians Consensus (AACP), and the Scottish Intercollegiate Network Guidelines (SIGN, based on SPAF).[69] [56,70,71] The risk factors described in these schemes are shown in table 2.1.

Table 2.1: Statistically Significant Risk factors for stroke in atrial fibrillation

Level of risk	Risk Classification Scheme			
	SPAF	**AFI**	**American College of Chest Physicians**	**SIGN**
High	Previous stroke/ TIA Women >75 years Systolic BP > 160 mmHg Left Ventricular Dysfunction	Previous stroke/ TIA Age≥65 years History of hypertension Diabetes mellitus	Previous stroke/ TIA Age>75 years History of hypertension Left ventricular dysfunction >1 moderate risk factor	Previous stroke/ TIA* Age>65 years plus one other risk factor:- Hypertension Diabetes Heart failure Left ventricular dysfunction
Moderate	History of hypertension with no other risk factors		Age 65-75 years Diabetes mellitus Coronary disease Thyrotoxicosis	Age> 65 years with no other risk factors Age<65 years with other risk factors
Low	No history of hypertension with no other risk factors	Age <65 years with no other risk factors	Age<65 years with no other risk factors	Age <65 years with no other risk factors

* SIGN classified previous stroke/ TIA as a separate 'very high' risk group

In addition to the schemes described above, the $CHADS_2$ scheme (Congestive heart failure, Hypertension, Age>75 years, Diabetes Mellitus and prior Stroke), an amalgamation of SPAF and AFI, also quantifies risk of stroke for those in AF according to the following risk criteria: prior cerebral ischaemia, history of hypertension, diabetes mellitus, recent congestive heart failure exacerbation and age≥75 years. [72]

Furthermore, data from the Framingham Heart Study has been analysed to produce a method of obtaining risk of stroke for people with AF.[73] Statistically significant ($p<0.1$) risk factors for stroke suggested by this work are advancing age (hazard ratio 1.34 per 10 year increment), female sex

(hazard ratio 1.73), increasing systolic blood pressure (hazard ratio 1.10 per 10mm Hg increment), prior stroke or transient ischaemic attack (hazard ratio 1.69) and diabetes (hazard ratio 1.69).

In summary, most studies of people with AF report the following as risk factors for stroke in AF: previous stroke/ TIA, age>75 years, history of hypertension, left ventricular dysfunction and diabetes.

c) Findings from literature on other risk factors for cognitive decline

Our search strategy was designed to look specifically for studies addressing cognitive decline. This search highlighted the following as major potential risk factors for cognitive decline:-

1. Hypertension

A large amount of work addresses the effect of hypertension on cognition and dementia: *The following studies suggested an association between hypertension and cognition:-*

- Data from the Framingham study [74-77] demonstrated that hypertension may be associated with reduced cognitive function, but only in subjects followed for a long period with no anti-hypertensive therapy.
- The Rotterdam study [78] found that silent cerebral infarcts were associated with hypertension , but not with diabetes and smoking or excessive alcohol consumption. Reports from this longitudinal study also describe an increased stroke risk in those with silent brain infarcts and white matter lesions, independent of major stroke risk factors. [79]
- A cross-sectional study [80] in the UK showed an association between hypertension and impaired cognitive function, with older patients with hypertension having impaired attention, short-term and long-term memory. Cognitive assessment scores were

significantly lower in hypertensive than normotensive groups. These groups were matched for age, educational level, depressive disorder and psychotropic medication.

- Further cross-sectional work found that higher diastolic blood pressure was associated with poorer performance on neuropsychological testing, and that this association was greater for younger than older subjects. [81]
- The Syst-Eur trial [6] demonstrated that in elderly people with isolated systolic hypertension, antihypertensive treatment was associated with a lower incidence of dementia. If 1000 hypertensive patients were treated with anti-hypertensive drugs for 5 years, 19 cases of dementia might be prevented. This study found that a reduction of 7mm Hg (systolic) and 3.2mmHg(diastolic) over four years halved the incidence of dementia.[82,83]
- The PROGRESS study found that cognitive decline reduced from 11% to 9% over 4 years in those taking perindopril and indapamine, due to prevention of stroke.[84]
- The Kungsholmen project, a longitudinal study of ageing and dementia [85] and other studies [86-88]; found that hypotension was associated with lower cognitive function and that systolic BP of at least 130 mmHg is important to the maintenance of cognitive functioning in the very old (>85 years). However, it also showed an association between severe hypertension that is not well controlled (systolic pressure >180 mmHg / diastolic >95mmHg) and poor cognitive function in this age group.
- The Honolulu-Asia Aging Study [86] showed that midlife systolic blood pressure predicts low cognitive function in later life. After adjustment for confounders (age, CHD, stroke, atherosclerosis), every 10mmHg increase in systolic blood pressure in mid-life led to a 5% increased risk of poor cognitive function in later life (mean age 78years). These findings are supported by data from the National Heart, Lung and Blood Institute Twin Study. [89]
- A prospective population-based study [90] showed that raised systolic blood pressure and high serum cholesterol concentration , and particularly a combination of these risks in

midlife, increases the risk of Alzheimer's disease in later life. This is further evidence for a role of vascular risk factors in the pathogenesis of Alzheimer's disease, not just 'vascular' dementia.

- Another prospective study demonstrated higher risk of cognitive decline in those with high systolic BPs. [91]

- Studies of the effect of antihypertensive therapy have demonstrated that it is safe and that treating hypertension is not hazardous to cognitive function.[92,93]

The following studies suggested no association between hypertension and cognition:-

- Analysis of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) [94] cohort demonstrated no relationship between blood pressure and cognitive function over a 6-year period of observation (after adjusting for age, sex and education).

- The Study on Cognition and Prognosis in the Elderly (SCOPE)[95] reported no significant difference in cognitive decline or dementia between those who did and did not receive an angiotensin receptor blocking anti-hypertensive treatment (candesartan), despite a slightly more effective blood pressure reduction in those who took candesartan.

Summary for hypertension as a risk factor for cognitive decline:-

There are conflicting results from different studies. There is more evidence for than against the hypothesis that hypertension is associated with cognitive decline, although the extent of this association is modest. In addition, it appears that any cognitive decline/impairment is related directly to hypertension, rather than antihypertensive drug therapy.

2. *Age*

A very large number of longitudinal studies demonstrated that older age is associated with cognitive decline. [77,96-99]

Of all the studies identified that have addressed the issue of age and cognitive decline, the majority have demonstrated an inverse association between age and cognitive performance. Only one study described lack of such an association between advancing age and cognitive decline in the majority of its cohort, finding this relationship only in women of below median intelligence. [77]

For most studies, analyses were primarily of changes in the cognitive function of the cohort over time. However, several of the studies also demonstrated that within the cohort, a small number of individuals did not deteriorate over time.

Summary for age as a risk factor for cognitive decline:-

Overall, the age of a cohort appears to be associated with a modest cognitive decline in the majority of people, though within study populations some individuals show no decline with age.

3. Cardiovascular disease

The Rotterdam study[100] demonstrated that atherosclerotic disease accounts for considerable cognitive impairment in the general population. Previous vascular events, presence of plaques in the carotid arteries and presence of peripheral arterial atherosclerotic disease were associated with worse cognitive performance (MMSE), independent of the effects of age and education. The Whitehall II study[101], a longitudinal study of British civil servants, found that angina, coronary heart disease and intermittent claudication were all associated with poor cognitive function.

Cross-sectional work[102] has demonstrated an association between congestive heart failure (CHF) of all NYHA classification grades and cognitive impairment (MMSE<24) , showing a 1.96 times increased risk of cognitive impairment for those with CHF (odds ratio 1.96; 95% CI: 1.07-3.58, p<0.028). Another study [103] confirmed that CHF was significantly associated with an increased likelihood of impaired cognition.

Another cross-sectional study [104] demonstrated that those with a left ventricular ejection fraction of less than 30% (i.e. systolic dysfunction) performed significantly worse on MMSE.

Hypercholesterolaemia has been shown to be associated with poor performance on memory tests. [90,105] Despite this, the MRC/ BHF Heart Protection Study of individuals at high risk of vascular disease demonstrated no significant differences in proportion with cognitive impairment, or mean neuropsychological test score, between groups who did and did not take simvastatin. In addition, similar numbers in each group went on to develop dementia. This finding was despite the fact that the simvastatin group showed a 25% reduction in deaths from vascular causes.[106] Similarly, the PROSPER (pravastatin in elderly individuals at risk of vascular disease) study found no effect of pravastatin on cognition,[107] and the Sydney Older Persons Study, a prospective study of those aged over 75 years, demonstrated a protective effect of hypercholesterolaemia for the development of dementia and cognitive decline.[108]

Summary for cardiovascular disease as a risk factor for cognitive decline:-

There is some evidence for associations between cognitive decline and previous cerebrovascular events, carotid artery plaques, peripheral atherosclerotic disease, vascular disease, CHF (all NYHA grades), left ventricular dysfunction and hypercholesterolaemia. However, these findings are

contradicted by the results of recent studies which found no effect on cognition of cholesterol-lowering therapy, and in one study a protective effect of hypercholesterolaemia.

4. Diabetes

A longitudinal study [98] demonstrated that cardiovascular disease and diabetes are associated with cognitive decline. Another prospective study also showed that diabetes in women was associated with cognitive impairment and decline. [109] Diabetes was shown to be associated with reduced performance on tests of abstract reasoning and visuospatial ability. [105]

Summary for diabetes as a risk factor for cognitive decline:-

There is some evidence suggesting an association between diabetes and cognitive decline and impairment.

5. Educational Level

Intelligence level as a young person may affect the extent and rate of cognitive decline with age, for example one longitudinal study [77] demonstrated that advanced age was only associated with cognitive decline in women of below median intelligence.

A cross-sectional sub-analysis of the Rotterdam study[100] demonstrated that lower (past) educational level was associated with poorer cognitive function.

The IOWA 65+ Rural Health Study, [110] a longitudinal study, demonstrated that educational level was associated cross-sectionally with cognitive test performance but did not predict cognitive decline. Another longitudinal study [98] demonstrated that a shorter duration of education was

associated with greater cognitive decline. Other prospective cohort studies reported that formal education had a protective effect against age-related cognitive decline, [111] with higher NART-predicted IQs being associated with less cognitive decline. [91]

A further prospective study reported that low educational level may also be a genuine risk factor for dementia (in addition to leading to increased detection on screening tests). [112]

The Nun Study, a longitudinal study of Catholic Sisters, found that cognitive function decreased with age at baseline, particularly in nuns without Bachelors degrees; whilst cognitive function declined over the follow-up period (1.6 years) to a greater extent in those nuns with Bachelor's degrees. A possible explanation provided was a healthy survivor effect in those without degrees, although it is not clear why this may be. [99]

Summary for educational level as a risk factor for cognitive decline:-

Most studies agree that a lower level of education is associated with poorer performance on neuropsychological tests. There is some conflict over the association with education and cognitive decline over time, with some studies showing less decline in those with more education; some studies finding no association; and others noting greater decline in those with more education.

6. Depression

Most work on depression and cognition has not been examined with longitudinal studies. However, one longitudinal, community-based study[113] explored this area and demonstrated that men and women with depressive symptoms were at increased risk of cognitive decline independent of insomnia. Another longitudinal study of factors predicting cognitive decline [77] demonstrated that depression was only associated with cognitive decline in women of below median intelligence and

men of above median intelligence. Possible explanations for this suggested vulnerability of women of below median intelligence to the negative influence of depression on cognition include biological explanations and deficiencies in metamemory skills (worldly knowledge reserves and ability to make pragmatic use of cognition) in this group.

Other prospective studies found an association between depressive symptoms and both cognitive impairment and cognitive decline. [114,115] Further work suggests a positive relationship between depression and subsequent cognitive decline, [116,117] but only in those with mild cognitive impairment at baseline. This study suggests that depression may occur early in the dementing process but may not itself be a risk factor for dementia.

Case-control studies [118-120] demonstrated an association between cognition and depression scores, but this study design makes it difficult to establish cause and effect. In contrast, another cross-sectional study [121] demonstrated no association between depression and cognition.

Summary for depression as a risk factor for cognitive decline:-

All identified longitudinal studies exploring this area found an association between depression and cognitive decline, although two of these studies found this association was only present in specific groups (according to intelligence or baseline cognitive function). Findings from cross-sectional studies were conflicting, with some showing an association between depression and cognitive impairment, and one study showing no association.

7. Use of medication

A small longitudinal study [122] demonstrated a significant decline in cognitive function associated with administration of some antihypertensive medication, although the SCOPE study[95] demonstrated no association between use of antihypertensive treatment with candesartan and cognitive decline or dementia.

Another study [123] demonstrates minor beneficial effects of the drug dihydroergocristine (an adrenergic alpha-antagonist and dopamine agonist) in reducing the risk of cognitive decline.

A longitudinal study[124] described how aspirin users, especially intermittent users, benefit slightly in having a reduced risk of cognitive decline.

Further prospective work has demonstrated an association between decline in memory and use of high dose non-steroidal anti-inflammatory drugs.[125]

A prospective cohort study found that those who used benzodiazepines at recommended or higher doses had significantly worse memory scores than non-users. [126]

Summary for medication use as a risk factor for cognitive decline:-

Studies demonstrate that some antihypertensives and benzodiazepines may increase the risk of cognitive decline or impairment, whilst dihydroergocristine and aspirin may reduce the risk of cognitive decline or impairment.

8. Lifestyle factors (Alcohol, smoking, exercise and diet)

A longitudinal study exploring predictors of cognitive decline [77] reported that neither alcohol nor smoking appear to be reliable predictors of change in cognitive function. This work also demonstrated that the number of cigarettes smoked daily was only associated with cognitive decline in women of below median intelligence.

Another longitudinal study[98] demonstrated that those who smoke and have cardiovascular disease (CVD) or diabetes may have a higher risk of cognitive decline, whereas those (with CVD/ diabetes) who drink moderate alcohol compared to abstainers may have a reduced or no alteration in risk of cognitive decline.

More longitudinal work undertaken as part of a larger study[127], the Canadian Study of Health and Aging (CSHA) demonstrated an association between alcohol abuse (using DSM criteria) and cognitive impairment. However, the Cardiovascular Health Study [128] found that consumption of up to six units weekly was associated with a lower risk of dementia compared to abstention.

The British Doctors Study[129], another longitudinal study, demonstrated that persistent smoking has little effect on the age-specific rate of Alzheimer's disease. An Australian study found no association between Alzheimer's disease or cognitive function and 'health habits' (exercise, smoking, alcohol use). [130]

An American longitudinal study found no significant relationship between smoking and the incidence of cognitive impairment, once data had been adjusted for age. [131] This conflicts with

work in Japan demonstrating a significantly higher risk of cognitive impairment in continuous smokers compared to never smokers. [132]

In addition, the Rotterdam study demonstrated no association between high dietary fat (total, saturated, cholesterol and trans fat) intake and increased risk of dementia,[133] and further work demonstrated no increased risk of dementia in those with a low body mass index (BMI).[134]

Summary for lifestyle factors as risk factors for cognitive decline:-

The evidence on lifestyle factors as risk factors for cognitive decline and impairment is conflicting. Of the smoking studies identified, only two demonstrated an association between smoking status and cognitive decline or impairment, whilst four demonstrated no association. Of the alcohol studies, one demonstrated an association between alcohol abuse and cognitive impairment, but two studies demonstrated no association and two studies showed a reduced risk of cognitive decline in those consuming moderate amounts of alcohol. The only study addressing exercise found this had no effect on the risk of Alzheimer's disease, and fat intake or BMI do not appear to affect risk of dementia.

9. Other risk factors for cognitive decline

- Insomnia: a longitudinal community-based study[113] observed that chronic insomnia predicts incident cognitive decline in older men.
- Ethnicity: a cross-sectional study (n=2,581)[135] observed that African Americans scored lower than Japanese Americans on the Cognitive Abilities Screening Instrument (CASI), this gap decreasing when only those within the high education groups were compared.
- A population-based cross-sectional study demonstrated that neighbourhood type (in this case suburban, transitional or barrio) has been shown to predict cognitive impairment. [136]

- Social disengagement (failure to maintain many social connections and participate in social activities) has been shown to be associated with risk of cognitive impairment. [137]
- A pooled analysis of four community-based prospective cohort studies demonstrated that women had a significantly higher risk of developing Alzheimer's disease (AD) after the age of 85 years than men, with no such increased risk of vascular dementia. [138] In contrast with this, the Cardiovascular Health Study found little effect of sex (or race) on incidence of dementia.[139]
- Genetic influences: a longitudinal study [140] observed a 45% pairwise concordance for decline on the Wechsler Adult Intelligence Scale (a test used to measure cognition) for monzygotic twins, and 8% for dizygotic twins.
- APO*E* Genotype: a prospective cohort study.[141] demonstrated that APO*E* 4 was significantly and uniquely related to lower score at baseline and significantly increased the odds of cognitive decline by 59%. Further work also demonstrated an association between APO*E* 4 status and cognitive decline, [142-145] and showed the use of oestrogen to provide some protection over cognitive decline in those with the APO*E*4 allele,[146] with a protective effect of hormone-replacement therapy in post-menopausal women.[147] Evidence also suggests that the combination of the *APOE* 4 allele and history of cerebrovascular disease, [148] and the combination of *APOE* 4 allele and midlife hyperglycaemia [149] may have a synergistic effect on cognitive decline.
- Evidence for an association between endogenous oestrogen levels and cognitive decline is unclear, with some studies demonstrating no association, [150] and others showing less risk of cognitive impairment in those with high oestrogen and low testosterone levels. [151] Other work describes no protective effect of oestrogen replacement therapy on age-related cognitive decline. [111,152]

- A small, prospective study has shown an association between cortisol levels and cognitive decline, with a non-significant inverse association between dehydroepiandosterone sulfate (DHEAS) levels and cognitive decline. [153]
- Studies of serum levels of the amino-acid homocysteine have shown no association between this and cognitive decline. This is despite the demonstrated association between homocysteine and increased risk of cerebrovascular and cardiovascular disease. [154]
- Residence: a longitudinal study [77] of factors predicting cognitive decline demonstrated that rural residence was only associated with cognitive decline in women of below median intelligence.
- High-grade stenosis of the left internal carotid artery, without history of stroke or TIA, has been shown to be associated with cognitive impairment and decline, even after adjustment for right carotid artery stenosis (thus reducing the likelihood that this finding is due to other vascular risk factors and atherosclerosis).[155]
- Participation in leisure activities has been shown to be associated with reduced risk of dementia in one prospective study.[156]
- Seropositive status for herpes simplex virus and cytomegalovirus has been demonstrated as being associated with cognitive impairment in those with cardiovascular disease.[157]
- Studies have demonstrated an association between low birth weight and poor cognitive function, although to date this has only been demonstrated up to early adulthood.[158,159]

Chapter 2 Summary

- To inform the work reported in this thesis, an extensive review of relevant literature was undertaken.
- I carried out three separate searches addressing; 1) studies of atrial fibrillation (AF), silent cerebral infarction and cognitive decline; 2) studies of the epidemiology of AF and 3) studies of other risk factors for cognitive decline.
- Strategies for searching electronic databases and grey literature were designed using recognised methodological filters. Selection of studies was done systematically. Study quality was considered when searching for literature, although a formal assessment of study quality is not reported here.
- There is evidence for associations between AF, silent cerebral infarction and cognition, but to date this has been largely from cross-sectional studies, including the pilot study [15] carried out prior to the work reported in this thesis. In order to adequately explore the aetiology of cognitive decline, longitudinal studies measuring cognitive function in representative populations over an appropriate period of time are needed. The work reported in this thesis is such a study.
- AF is a common condition, the prevalence of which increases as the population ages. Studies of people with AF report previous stroke/ TIA, age>75 years, history of hypertension, left ventricular dysfunction and diabetes as risk factors for stroke in AF. It is plausible that these may also be risk factors for silent stroke leading to cognitive decline in those with AF.
- Despite the proven efficacy of anticoagulant and antiplatelet therapy in preventing stroke in people with AF, there is significant underprescribing of these treatments. The work reported in this thesis addresses the role of anticoagulant and antiplatelet therapy in preventing cognitive decline in addition to stroke.

- There are many studies of risk factors for cognitive decline other than AF. The most widely studied risk factor is hypertension, for which evidence suggests there may be a modest association with cognitive decline. There is also strong evidence supporting the association between age and cognitive decline.
- There is more scanty literature supporting an association of cardiovascular disease, diabetes, depression, education, medication and lifestyle with cognitive impairment.
- Knowledge of the existing work on risk factors for cognitive decline, obtained through the literature searches described here, provided a sound base on which to design the method for the study (the Cognition in Atrial Fibrillation Evaluation) described in this thesis.

Chapter 3 – The Epidemiology of Cognitive Decline

- Part 1: Literature search method
    - Purpose of the search
    - Objectives
    - Search strategy
    - Criteria for inclusion
    - Data extraction
    - Assessment of study quality
    - Data synthesis
- Part 2: Findings from the literature
    - Cognitive function research methodology
    - Pathogenesis of cognitive decline
    - Incidence and prevalence of cognitive decline
- Part 3: Results of the formal systematic review
    - Key findings
    - Issues arising from the formal systematic review, including critical appraisal
- Chapter 3 summary

Part 1: Literature search methodology

Purpose of Search

In order to study the role of atrial fibrillation in the aetiology of cognitive decline, it was vital to have a thorough understanding of the nature of cognitive decline in the general elderly population, i.e. to what extent would we expect cognitive decline in the general population? To explore this further I undertook a formal systematic review of the rate and nature of cognitive decline in the general elderly population.[160] Part of this search formed a component of an MSc in Health Sciences.[161] In addition to the formal systematic review, other literature of relevance was identified to complete the understanding of the epidemiology of cognitive decline.

Objectives

The objectives of the systematic review were:

(i) To systematically obtain and appraise all of the relevant literature on cognitive decline in the general elderly population; (ii) to collate the main findings following appraisal of the literature; (iii) to present a systematic description of the current literature, with comment on the quality of studies included; and (iv) to identify issues of relevance to the work reported in the main body of this thesis, that is the Cognition and Atrial Fibrillation Evaluation (CAFÉ).

The objectives of the less formal search on epidemiology of cognitive decline were to summarise the natural history of cognitive decline and to identify issues in the study of cognitive decline that would be relevant to CAFÉ.

Search strategy (Appendix 1):

Before the review, literature searches on methods of systematic review and cognitive function research were conducted in order to inform study design. This highlighted issues such as the

association of cognitive decline with increased mortality, the numerous different tools used to assess cognitive function and the reliability of estimates of change. In addition, it was clear that there was limited literature on the *clinical* significance of declining scores on neuropsychological tests.

As for the searches described in Chapter 2, the McMaster strategies for aetiology, causation and harm[26,27] were combined with the core section on cognitive decline and dementia from the Cochrane Dementia and Cognitive Impairment Group (CDCI)[28]. This detailed, combined, electronic search strategy was then applied to Medline (1966-2000), Embase (1990-2000) and PsycINFO (1984-2000). This search strategy was effectively the same as that undertaken for search 3 in chapter 2, although the inclusion criteria for screening abstracts were different (see below). The identification of abstracts from electronic databases was designed to be maximally sensitive in order to minimise the possibility of overlooking relevant articles. In addition a search of web resources and grey literature was undertaken.

Criteria for inclusion:

Based on the literature review, it was decided that participants of included studies should be predominantly aged 60 years and over and should be a representative community sample. They should not be subgroups of the population selected on the basis of existing specific illness.

Included studies should be designed as community-based, prospective cohort studies, with high rates of follow-up. These criteria were incorporated into a protocol for screening of the abstracts generated by the search of electronic databases, which was modified slightly after piloting by two reviewers (myself and Dr Janice O'Connell, who acted as second observer for several stages of the review).

I then used the protocol to select those abstracts for which full text paper retrieval was appropriate. This included studies for which the abstract was not sufficiently detailed to allow evaluation of inclusion criteria. To increase the objectivity and consistency of the decision to include or exclude a paper based on reading the full text, an 'In/Out' form (Appendix 2, Box 1) was developed and piloted (HP, JO'C, RT). Where there was uncertainty, the abstracts were discussed with a second and third observer (JO'C, RT) and a medical statistician (AH). In five cases it was necessary to correspond with the original author. The review was not blinded to author / journal / title, since this would have been logistically difficult [162,163] given time and resource constraints.

Data extraction

The data extraction sheet (Appendix 2, Box 2) was derived from the Centre for Reviews and Dissemination's example data extraction sheets for reviews of effectiveness, [164] but in addition we incorporated quality measures and recommendations from the literature on critical appraisal of cohort studies. [26 35,70,165] The sheet was piloted, modified and implemented. Although the rate of cognitive decline was the primary outcome measure, I also extracted data which could form the basis of quality appraisal of the research, and also information to enable meaningful comparisons between cohorts.

Assessment of study quality

When an estimate of methodological quality of reviewed studies is incorporated into a review, the interpretation of the findings can alter. [166] There is no consensus on the appropriate method of grading the quality of studies used in systematic reviews.

Based on a search of the literature on quality appraisal and cognitive decline study methods described above[26,35,70,167-169] key criteria were selected relevant to cohort studies of cognitive decline: i) that the study sample was well defined and representative; ii) that the period of follow-

up was sufficiently long to allow cognitive decline to occur; iii) that loss to follow-up was minimal; and iv) that outcome criteria were objective and unbiased. Providing that a study met these criteria or addressed them satisfactorily, the study was included in the review. An appraisal checklist and quality assessment form, again based on the literature search, were designed and piloted, incorporating three main headings (participants and setting, methods and analysis, and results – Appendix 2, Box 3). The appraisal checklist addressed the quality criteria as described, with the selection of 'good', 'fair', or 'poor/not reported' for each of the three headings. This checklist and quality assessment form was then applied to all studies included in the review, to further evaluate each study.

Data synthesis

A data-extraction spreadsheet was developed, using information from the data-extraction form.

The final decision on how best to combine the results was made after summarising the results of the different studies. The predefined options for combining results included meta-analysis of published results, pooled analysis of primary data or narrative review [170]. The former two options are more objective, since they use explicit criteria and can be reproduced scientifically to provide a quantifiable result. [35] However, as with much research, [171] the studies were heterogeneous in terms of participant's populations, countries of origin, and neuropsychological tests employed. Thus it proved impossible to pool or combine the data by meta-analysis. In addition the length and number of follow-ups between studies were different, with varying proportions lost to follow-up. Hence narrative review was the most appropriate method for presenting summary information. Reviewing the differences between studies in this manner helped to distinguish between the important effects of true diversity and variations due to confounding and bias. [171]

Part 2: Findings from the literature

The principal outcome of interest to CAFÉ is reduced cognitive function in people with NVAF, but because one of the proposed underlying pathophysiological mechanisms is silent cerebral infarction, the discussion here also includes a commentary on the literature on silent infarction. Although the search strategy included literature on Alzheimer's disease, this chapter focuses on the findings of the literature on vascular dementia, vascular cognitive impairment and cognitive impairment/dementia due to mixed aetiologies, since these areas are of most relevance to this thesis.

Cognitive function research methodology

Outcomes from cross-sectional versus longitudinal studies:

Williams [172] suggests that the association between cognitive decline and age was more strongly demonstrated when the cohort was analysed at a cross-sectional level than when the same participants were analysed over time (after repeated long term follow-up). Hence cross-sectional studies of associations between age and cognition may over-estimate the true association. Cross-sectional studies are not able to adequately assess aetiology and causation. The ideal epidemiological study to explore these areas would be an inception cohort study of a representative population. [14]

Different tools used to assess cognitive decline:

It is apparent that even in the diagnosis and assessment of cognitive decline and dementia, there is no single mental status test or battery of tests which is recommended by all guidelines, neither nationally nor internationally. [173]

The effect of cognitive impairment on mortality:

Moderate and even mild cognitive impairment (defined as a score of 24 to 27 on the MMSE) has been shown to be associated with increased mortality. [174,175] In addition, vascular factors have been shown to predict drop-out rates in some cohort studies, therefore individuals who may be at greatest risk of cognitive deterioration are more likely to be lost to follow up. [176]

The effect of cognitive impairment on general activities:

Further work based on the Canadian Study of Health and Ageing [177] reinforces the association between cognitive decline and age-related functional deficits, demonstrating that people with cognitive decline are 'functionally older' (e.g. in terms of gait, mobility problems, activities of daily living and cardiovascular problems) than those without cognitive decline.

Institutionalization of those with cognitive impairment:

Cognitive impairment and dementia are important causes of institutionalisation in the elderly, [178,179] therefore studies which exclude those living in such institutions at baseline or follow-up are likely to have a selection bias resulting in misleading estimates of the rate of cognitive decline in the general elderly population. In addition, studies which include only institutionalised groups may inadvertently (or deliberately) select patients according to factors such as severity of impairment and the interests of the institution. [180]

Age associated memory impairment (AAMI):

Several studies used subjects with AAMI as their target population. AAMI is a term proposed by the National Institute of Mental Health (NIMH) in the USA. The criteria for AAMI are: 1) memory test performance of at least one SD below the mean observed for young adults; and 2) intact

general cognitive function as measured by instruments such as the MMSE. Up to one third of healthy 60 to 78 year old subjects meet the NIMH criteria for AAMI. [181]

Length of follow-up and reliability of estimates of change in test scores:

Several studies have demonstrated improvement in cognitive function in early follow-up assessments,[333] for example at one year, followed by subsequent decline or stability. Possible explanations for such findings include learning effects in the follow-up assessment and higher anxiety in the first assessment, and it is also likely that regression to the mean has taken place. In addition, Van Belle's work [182] demonstrates that the reliability of estimates of change with certain neuropsychological tests (for example the MMSE) is likely to increase with a longer duration between assessments. He also demonstrates that estimates from a single instrument over a short time period are less reliable than if such results were combined with the results of other tests.

Pathogenesis of vascular cognitive impairment and decline

Published work demonstrates that a degree of cognitive decline is almost universal in those aged over 60 years. However, there is always some individual variation, and those with better cognitive functioning at baseline tend to have less decline. [183]

Normal ageing results in degenerative changes (senile plaques, neurofibrillary tangles in the hipppocampus), an increasing number of small, silent vascular infarcts and loss of up to 50% of cortical synapses. This may lead to a reduction in brain reserve capacity, following which only minor lesions could result in dementia.

The Rotterdam study [78] demonstrated that 24% of non-demented participants had one or more cerebral infarcts on MRI, of which 83.8% were silent rather than clinical. Skoog found that vascular factors (stroke and stroke risk factors) are present in more than 50% of dementias. [184] In addition, vascular dementia related to stroke is the second most common cause of dementia after Alzheimer's disease. A recent study demonstrated an association between silent cerebral infarcts and history of atherosclerotic vascular disease (without history of stroke or TIA).[185]

There is a range of pathological definitions, from 'multi-infarct dementia' – due to large and small strokes, to the broader 'vascular dementia' which includes other types of cerebrovascular disease associated with dementia, to 'vascular cognitive impairment' that includes the milder end of the spectrum. [186] In addition, dementia can be due to many small infarcts ('multi-infarct') or a single/ several larger infarcts in specific areas of the brain controlling cognitive function (strategic-infarct dementia). Furthermore, a recent study has demonstrated an association between cognitive status and cortical microinfarcts and demyelination.[187] Costs of carrying out detailed brain imaging (e.g. MRIs) mean that most research has focused on multi-infarct dementia, ignoring ischaemic white matter lesions.

Often mixed pathologies result in dementia. Approximately half of vascular dementias may be pure (i.e. no evidence of Alzheimer's type pathology).

Cognitive impairment due to vascular pathology covers a range of disease severity from dementia (including VaD, AD and mixed AD[186,188] to cognitive impairment with no dementia (CIND). Approximately 46% of those with CIND develop dementia within 5 years[8]. It is suggested that whether or not CIND progresses to dementia can partly be predicted by sex (women are at greater

risk of dementia) and possibly by performance on neuropsychological testing (poor performance on tests of memory and category fluency being associated with incident dementia).[8]

Classification of vascular dementia may be as follows [186,189]:- i) large vessel dementia affecting the carotid artery, circle of Willis and larger meningeal branches; ii) multi-infarct dementia / strategic infarct dementia affecting the anterior circulating artery and middle circulating artery territories, the thalamus, basal ganglia, basal forebrain, and the angular gyrus (AF may predispose to this type); iii) small vessel dementia affecting intra-cerebral arterioles, of cortical and / or subcortical sub-types (both are associated with hypertension and arteriosclerosis); and iv) hypoxic-ischaemic hypoperfusive dementia, where a temporary reduction in blood supply results in tissue damage - although the brain has autoregulatory mechanisms, interruption to blood supply is likely to be general, resulting in a global encephalopathy, with focal lesions in vulnerable areas. AF may predispose to both small vessel dementia and hypoxic-hypoperfusive dementia. Classification schemes for vascular cognitive impairment (other than according to primary vascular aetiology as described above) include categorising the dementia according to type of ischaemic brain lesion (e.g. lacunar infarct); according to anatomical location of brain lesions (e.g. cortical); and according to primary clinical syndrome (e.g. defined brain areas).

Evidence suggests that mild cognitive impairment often precedes both vascular dementia (particularly where the pathology is predominantly small vessel disease rather than multi-infarct or strategic-infarct dementia) and Alzheimer's disease. [190]

The pathogenesis of decline in cognitive function with age may be related to a variation between individuals in the presence, severity of and rate of change in white matter hyperintensities. The presence of periventricular and deep white–matter hyperintensities has been shown to be associated

with a decline in performance IQ in the 70 to 80 years age group. [186] However, this only explains a small proportion of the wide variation in cognitive decline related to age.

Incidence and prevalence of vascular cognitive decline

There is a lack of consensus on what the diagnostic criteria should be and how they should be used in research, making it difficult to compare figures for incidence and prevalence described here:[186]

Prevalence

Geography: The proportion of people with vascular dementia among those with any dementia varies from 11% (Spain) to 45% (Sweden) in Western European studies, and is thought to be generally higher in Asia, former Soviet Union and Eastern European countries. However, this may be due to different diagnostic criteria, and possibly age differences in those recorded. In addition, the previously high proportion of vascular dementia in Japan may be reversing to the European and North American trend, due to societal changes +/- diagnostic changes. Urban versus rural living also plays a role, for example there are higher rates of vascular dementia in Beijing, where there is higher salt intake and higher hypertension prevalence, than in the more rural Shanghai, where Alzheimer's predominates.

Sex: Vascular dementia has a higher reported prevalence in men than women (contrasting with AD, especially after 80years), especially in those under the age of 75 years. [184,191,192]

Effect of better stroke management: there is no indication that the prevalence of vascular dementia is decreasing, despite better treatment of hypertension and a decline in stroke incidence. This may be partly explained by the ageing population, but also an increase in stroke survivors. Thus paradoxically, better treatment of stroke may have led to higher prevalence of vascular dementia.

Vascular dementia prevalence rises with increasing age, although less steeply than for Alzheimer's disease. Therefore we can conclude that the ageing population will lead to an increase in the number of vascular dementia cases.

Incidence

Vascular dementia and AD differ in duration of disease and survival, for example reported mortality in vascular dementia is higher than Alzheimer's. Because of this, vascular dementia may make a bigger contribution to dementia incidence than prevalence. Therefore incidence studies are preferable to prevalence studies.

However, there are few incidence studies in general, possibly due to decreased resources and short-term research funding policies, and particularly few studies of incidence of vascular dementia.

The incidence of vascular dementia rises steeply with age up to 90 years or more, but less steeply than Alzheimer's disease; therefore survival differences are not likely to be responsible for this effect. The Rotterdam study demonstrated a levelling off of incidence in vascular dementia in the oldest age categories, compared to a steep increase with age for Alzheimer's disease incidence. [78] This could be due to the 'healthy survivor' effect.

Sex: as for prevalence, men have a higher incidence of vascular dementia at younger ages (and higher than women at all ages), and women have a higher incidence of Alzheimer's at older ages.

Part 3: Results of the formal systematic review

Many studies were identified which addressed cognitive decline in the general elderly population, but only 19 met the inclusion criteria for this review. Studies addressing cognitive decline in the general elderly population were clinically and methodologically heterogeneous. In particular, the lack of an international gold-standard battery of neuropsychological tests prevented quantitative combination of study results. Therefore the review was unable to establish the precise rate of cognitive decline in the general population, as originally intended. When studies using the same neuropsychological tests were grouped together , the rate of decline varied greatly between studies. This variation in performance cannot be explained by differences in age. The study cohort with the greatest annual decline in Mini Mental State Examination (MMSE) score was also the oldest group.[193] However, for the remaining studies using this test there was no relation between age of the cohort and MMSE rank. Furthermore, age of the cohort had no obvious effect on Cambridge Cognitive Examination (CAMCOG) rank in studies employing that test. Quantitative comparison of these particular studies was not possible due to heterogeneity of the participants.

Key findings:

Although it was not possible to combine the results, the extraction and summary of data from each study was performed. This led to the following key findings:

Cognitive decline is almost universal: most of the studies which did not exclude those with dementia demonstrated significant decline for the whole sample over the study intervals, although two studies described very small changes[194,195] in the whole sample. Studies excluding people with dementia showed smaller rates of decline, although in most cases these were still statistically significant. All of the studies which addressed the effect of age on cognition noted that the rate of cognitive decline increased as age at baseline increased. In addition, those which analysed the effect of baseline cognitive function found an inverse association between this and the rate of cognitive decline. Despite these group observations however, intra-individual variation in the rate of decline was also described, regardless of predictions based on factors such as age or initial cognitive function. Even where there was a statistically significant trend towards an association between increasing age and increased cognitive decline, a proportion of individuals demonstrated no such change in cognition. Although the majority of studies reported only mean declines in subgroups, some studies described the proportion of participants whose cognition was unchanged; 15% of the participants in the Cambridge Project for Later Life (CPLL)[196] had unaltered cognitive function, and a further 28% improved over the mean 28 months follow-up. 32% of the participants in Epidemiologic Catchment Area (ECA) study [197] demonstrated no change or improvement in cognitive function during the mean 11.6 years follow-up.

Quality: Following appraisal of the included studies, whilst all met core inclusion criteria the quality otherwise varied between studies. The quality criteria with highest overall scores were the effectiveness of the studies' analyses to account for the passage of time, where 18 out of 19 scored 'good'; and the adjustment of the analyses for prognostic factors/confounders, where 12 out of 19 scored 'good'. Quality criteria for which studies scored poorly were the reporting of a power calculation, where 16 out of 19 scored 'poor/not reported'; and whether or not an appropriate, trained professional carried out the neuropsychological testing, where 9 out of 19 scored 'poor/ not reported'.

Overall, one of the most important limitations in the studies included in this review was high loss to follow up, varying from 16.9% at best and 93.3% at worst, with obvious potential for non-response bias. Since cognitive impairment has been shown to be associated with increased mortality [174,175] individuals who are declining are more likely to be lost to follow-up[176], such that high attrition rates in longitudinal studies may lead to considerable under-estimate of the true rate of cognitive decline in the very old. [174,175,198] Although difficult in this age group, such bias could be minimised by future studies through maximising the completeness of follow-up. Interestingly, for studies included in this review, the proportion of participants lost to follow-up does not correlate with the annual rate of cognitive decline when studies using MMSE are compared. In the same way, loss to follow-up does not strongly correlate with annual rate of decline in studies using CAMCOG. Adjustments for the effect of attrition need to be made in studies of elderly cohorts, before true decline can be estimated. One way in which this has been done is by assuming a linear decline in scores over time, then extrapolating the rate of decline at interim assessments for participants who have been lost to later follow-ups[198]. In this way missing data can be incorporated into the main analysis or sensitivity analyses.

In addition, the type of neuropsychological test used in some cases was likely to be insensitive to minor changes in cognition, and in others was not widely used within the field, with minimal literature to support validity.

Issues arising from the formal systematic review, including critical appraisal

The initial aim of the review was to focus only on studies which included a representative sample of the community, incorporating those who suffer from dementia. It became clear that some studies excluded those with dementia at baseline, but met every other criterion for inclusion in the review, and were therefore included. By including both types of study in the review and appraising them separately, more useful information has been gathered.

Literature is scanty on what constitutes a clinically significant decline for most of the neuropsychological tests used. The studies included in this review commented only vaguely on the significance of their findings in relation to the general population, making interpretation of results very difficult. Better understanding of clinically significant cognitive decline is crucial to the design, conduct and interpretation of the results of research studies and the implementation of their findings into clinical practice.

A number of potential biases within the review methodology were possible. [35,199-203] The decision taken to only include articles written in English, and 'file-drawer phenomenon', [199] where researchers are less likely to submit non-significant research for publication, may have contributed towards publication bias in this review. An attempt was made to reduce such bias by including grey literature searches. The possibility of inclusion and information bias was tackled by setting specific, explicit criteria for inclusion at the onset; contact with lead researchers in the field; and the

use of second observers, checklists and protocols to ensure implementation of specific and explicit criteria was intended to reduce selector, observer and interpretation biases. However, I was the only observer who extracted data from included studies and formulated conclusions, thus there is potential for interpretation bias. Quality scoring bias may occur if methods and criteria for assessing quality are not established from the outset, such that the study quality appraisal may be influenced by the studies retrieved. This review tackled such bias by establishing an appraisal checklist prior to study selection.

I chose to present cognitive decline and duration of follow-up as mean values for most studies, since these were the only available results. However, median values may have been more appropriate since some of the data may be skewed (i.e. non-normal). The effect of generation demonstrated by one of the studies [204] suggests that cognitive performance depends not only on ageing and but also birth-cohort generation-specific factors. This suggests that test reference values may soon become outdated and should be regularly reassessed. In addition, test norms should be used with caution if examiner factors are likely to influence test results.

It was apparent from the included studies that there was almost universal cognitive decline in the elderly, though this was small in those with good functioning at baseline. This suggests that cognitive decline is an important condition and it is crucial to explore potential aetiological factors such as atrial fibrillation.

The lack of a "gold standard" battery of neuropsychological tests made choosing a battery for CAFÉ difficult. Ideally a consensus should be reached among researchers in this field, aided by a systematic review of neuropsychological tests with reference to validity, reliability, clinical significance of change and relevance to appropriate cognitive domains, for which further primary

research may also be required. This could be made possible by the influence of grant-giving bodies, who may encourage collaborative research and recognise specific neuropsychological test batteries with demonstrated validity and reliability. In addition, international professional groups such as the International Psychogeriatric Association could encourage establishment of a consensus on appropriate design and conduct of studies in the field and standardisation of neuropsychological tests.

Chapter 3 Summary

- A comprehensive review of the literature on the epidemiology of cognitive decline consisted of a formal systematic review of cognitive decline in the general elderly population. In addition specific searches for literature covering issues of relevance to the work reported in this thesis were undertaken where appropriate.
- A number of issues in cognitive function research methodology were identified, including the challenge of high attrition rates in elderly populations, the need for longitudinal studies when looking at change over time and the effect of cognitive function on mortality leading to survivor bias.
- Pathological classifications of cognitive decline include vascular dementia, Alzheimer's disease and mixed dementia. Prevalence and incidence of dementia varies according to sub-type and geography.
- Key findings from the systematic review were that cognitive decline is almost universal, that quality of studies in this area varies widely, that studies in this area are vulnerable to bias, particularly selection and survivor bias, and that there is a need for a gold-standard battery of neuropsychological tests in order to make studies of cognitive decline comparable.

Chapter 4– Neuropsychological tests used in the CAFÉ study

- Selection of the CAFE neuropsychological test battery
- Literature search on CAFE neuropsychological tests
  - Purpose of search
  - Search strategies
  - Literature search findings
    - — Key characteristics of CAFE neuropsychological tests
    - — Sensitivity literature
    - — Clinical significance and normative data
    - — Correlation with NART scores
- Chapter 4 summary

Selection of the CAFE neuropsychological test battery

Measurement of cognitive function can be approached in many different ways. This in itself can cause problems, since different studies therefore use varying approaches, reducing homogeneity and thus making it more difficult to compare results. [169]

CAFE used the same neuropsychological test battery as the pilot study described earlier [15]. This battery had been validated, and contained nine components which measured general cognitive function, pre-morbid intelligence, verbal long term memory, short term memory, information processing and attention, selective attention, divided attention and non-verbal memory. This battery was selected because it was pen and paper based and therefore portable. In addition, the battery could be administered in one hour, was appropriate for an elderly cohort, and it was relatively easy to train the research doctor and nurse to administer the battery.

The CAFE neuropsychological test battery contained widely used components including: the Rey Complex Figure,[205] primarily a measure of non-verbal memory and visuo-spatial ability; the Mini Mental State Examination (MMSE), [182,206-208] a measure of general cognitive function; the Logical Memory and Digit Span subtests of the Wechsler Memory Scale (WMS) [209-211] which measure short and long-term verbal memory and attention; Map Search and Telephone Task subtests of Tests of Everyday Attention, [212,213] which measure selective and sustained / divided attention; and the Paced Auditory Serial Addition Test (PASAT), [291,311] principally a measure of information processing and attention.

In addition, the National Adult Reading Test (NART), [214,215] a measure of premorbid intelligence, made it possible to determine whether or not performance on other tests was influenced by intelligence level.

The battery was developed to assess cognitive impairment due to cerebrovascular disease, by Professor Ian Robertson at the Medical Research Council Cognition and Brain Sciences Unit in Cambridge.

Literature Search on CAFE neuropsychological tests

Purpose of search

This search was undertaken to fully inform the design, conduct, analysis and interpretation of findings of the study, since the neuropsychological tests used formed the basis of the primary outcome measure of the study.

Search strategies

An extensive literature search was undertaken to identify papers examining the subtests of this battery in terms of: i) clinical significance; ii) sensitivity in measuring change over time; ii) construct validity. Medline was searched between 1966 and (most recently) March 2004.

Literature search findings

1. *Key characteristics of the neuropsychological tests within the CAFE battery*

Findings from the literature search on key characteristics of the different components of the battery are reported here, focusing on clinical significance, reliability in measuring important differences and reliability and validity in measuring change over time. In addition, a table to help with orientation of direction of test scores, a table summarising cognitive domains of the tests, and documents used to carry out Rey Complex Figure, Map Search, Telephone Task and NART are provided in Appendices 3 and 4.

a) Mini mental state examination (MMSE)

i) Literature on clinical significance or clinical importance.

With retest intervals of 1-2 years, normal people show about 2 points of change and retest correlations are lower (<0.80) than for shorter intervals.[216 217] Therefore caution is needed in interpreting small changes in scores. Those with dementia show an annual decline of 2-3 points [216]

Modest correlations have been demonstrated between MMSE and functional capacity, such that a score of 26 or below may signify functional impairment (e.g. cooking etc). [216] Although intellectual impairment is considered if the score is 23 or less, only one third of those with this score were diagnosed with dementia in one community study. [218]

Change in MMSE over time has been shown correlate with decline in other cognitive function tests when measured in the general elderly population, with increasing decline in the oldest old (>80yrs).[208]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

MMSE has been shown to be sensitive to dementia and good at predicting AD and more severe cognitive decline, although is less sensitive to very mild cognitive decline. [216] In addition, there is evidence that MMSE is a poor predictor of conversion to dementia[219].

The test-retest reliability and interrater reliability have been shown to be inadequate in detecting small changes in cognitive function (such as response to new drug therapies), with a true change only detected reliably if it was of at least three points[220]. Other work demonstrates high interrater reliability for the Modified-MMSE, with high test-retest reliability over 3 years[221], and there are further reports of high interrater reliability (above 0.65). [206,216] Internal consistency estimates are reported between 0.31 (community samples) and 0.96 (secondary care samples).[206,216]

This test is very widely used, and is proven to be valid and reliable to assess cognitive function on a cross-sectional basis[206,207], except for those with very severe dementia where discrimination is lost. However, although valid as a measure of general cognitive function, it does not show validity for accurately measuring specific cognitive domains without further neuropsychological tests (attention, copy and memory are sometimes suggested)[222]. Reliability appears to depend on length of observation period, with demonstrated reliability coefficients for change in MMSE at six months of 0.16 and at 2 years of 0.75. MMSE reliability is suggested as reasonable if the period of observation is greater than one year[182].

In addition, MMSE has been shown to be reasonably reliable when studied in those with progressing dementia [182], providing that the length of time between observations is one year or more.

iii) Other issues

- MMSE components include orientation, registration, attention and calculation, immediate memory, short-term verbal memory recall and 'subtracting serial sevens', a test of mental tracking. However, it is inappropriate to use MMSE to measure a specific domain since it is not adequately sensitive [223].
- MMSE is not educationally biased (i.e. the score is not greatly influenced by level of education of the participant) regarding reliability and construct validity[224], but is educationally biased as a screening test predicting dementia (eliminated by having a 2 point higher scoring cut-off for those with more education i.e. above primary school).
- MMSE has been shown to be related to premorbid intelligence (correlation coefficient with NART is 0.56 and education, and also decreases with advancing age, although race, ethnicity, social class, gender and depression are thought to have little effect. [216]
- Disadvantages of MMSE include ceiling effects, with the maximum score of 30 being easily achievable in those without cognitive impairment.
- MMSE is often part of a test battery (e.g. CAMCOG and CERAD- Consortium to establish a registry for AD). [225,226]

b) National adult reading test (NART)

i) Literature on clinical significance or clinical importance.

Although a stated measure of premorbid intelligence, thus being deliberately insensitive to early dementia (Spreen), NART has been shown to deteriorate in moderate/ severe dementia, with degree of underestimation increasing with severity of dementia, and can underestimate IQ in those with mild dementia with linguistic problems. [216,225,227] In addition, some report that NART scores decline even in the early stages of dementia.[228,229] NART has not been standardised on an elderly population, and is a poor discriminator for those with very high or very low intelligence.[218]

However, when those with and without cortical atrophy were tested, NART score was not significantly different between the two groups, [218,230] and other studies of dementia found that NART score stayed the same throughout the observation period [218,231,232] with only a few studies showing deterioration in NART[218,233] and one study showing stability of score in those with mild dementia and deterioration in those with moderate/severe dementia.[234]

Overall, it appears that NART is correlated with disease severity, [228,235] declining with disease progression. [228,236]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

NART has been shown to be very reliable [218,237] with demonstration of high interrater reliability [232] and high test-retest reliability.[218,237]

NART has been shown to be strongly associated with current cognitive status (using MMSE and CAMCOG), supporting its acceptability as a measure of premorbid intelligence[238]. Further work demonstrates its' reliability in predicting premorbid intelligence[239]. NART has been shown to be reliable over time, with high test-retest reliability over 7 years[240]. Other work demonstrates reliability of change in NART over time for those with no dementia /minimal/mild dementia[215], although less reliability and need for correction using MMSE score for moderate or severe dementia [214,215,241].

Further studies describe no variation of change in scores with age [208], supporting the usefulness of NART as a measure of pre-morbid functioning. [238]

This test has been very widely used and there is considerable evidence for its reliability on a cross-sectional basis. Practice effects are reported to be statistically significant but very small.[216,218] NART correlates with education (r=0.51) and social class (r=0.36), [225] with no gender differences. [225] Moderate to good correlations have been demonstrated between NART IQ and measures of general intellectual ability (0.4 to 0.8) [216] [242] and education. [216] NART has demonstrated validity as a measure of intelligence,[218] with evidence for good construct validity,[237] and has been shown to be a predictor of some components of WAIS-R.

iii) Other issues

- Since measurement of change is a fundamental component of the CAFE battery, it is also useful to take one measurement which is relatively insensitive to change. For this study, the NART was selected because it is the most commonly used estimate of premorbid intelligence. Correlation of performance on the NART with performance on the other subtests made it possible to determine whether intelligence was confounding the results. The *New* Adult Reading Test (NART) is the version used for CAFE. [216]
- NART is based on the observation that the ability to read irregularly spelled words remains intact in mild dementia.
- NART has been standardised against WAIS-R. PASAT score can be predicted from NART and age (PASAT = 215.74 – (1.85xNART) – (0.77xage),[216,218] and NART has also been shown to correlate with WAIS-R (0.72).[216,225,243] Others report that although NART can be useful in estimating verbal premorbid intelligence and learning, it does not improve estimation of other neuropsychological domains[244].
- The Cambridge Contextual Reading Test (CCRT) sets the NART in semantic and syntactic context and is demonstrated to show higher prediction of premorbid intelligence than NART in those with mild/ moderate dementia[245]

- Some use demographic information (education, sex) in conjunction with NART errors to arrive at IQ. [216,218,239]
- NART has been used in many other test batteries. [225]

c) Wechsler Logical Memory test sub-test of Wechlser Memory Scale - Revised (WMS-R)

i) Literature on clinical significance or clinical importance

The literature search found no reports on clinical significance of performance on the Logical Memory test, except for one report that an average gain in score of 1 point after one year in a young group, [225,246] and 0.7 points in one year in an older group (mean 69 years) may be expected due to practice effects.[225,247]

This test measures memory functions which are equally represented in both hemispheres, therefore damage to one side of the brain only (e.g. unilateral silent infarcts) may have no effect on the performance of this subtest.[225]

The Logical Memory subtest has been shown to distinguish those with dementia from those without [248] and discriminate between those with dementia and those with an evolving dementia; but not to predict which elderly subjects with early memory complaints would develop dementia.[249] In addition, the test has been shown to be sensitive to detecting dementia of Alzheimer's type [216,250]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

The Wechsler Memory Scale (WMS) has been widely used since 1945 [209], and therefore there is much published literature reporting high test and re-test reliability [210] and construct validity [211].

The WMS has been shown to decline over time, with largest decline in those with shortest survival time at age 70 or over. [251] Another prospective study described no significant change in the score in a sub-group of the general elderly population who did not go on to develop dementia. However, it also demonstrated that the logical memory subtest declined prior to the onset of detectable clinical changes in the whole sample. [252]. Further prospective work suggests that the Logical Memory and Digit Span tests are highly sensitive to early cognitive decline, and can differentiate between normal elderly subjects and those who later go on to develop dementia [253].

There are some reports of practice effects in repeated administrations with the Logical Memory test[254], and there is potential for bias due to priming patients toward correct or incorrect responses.[255] However, high interrater reliability has been demonstrated specifically for the verbatim scoring approach that was adopted for the CAFE study [256] Reported reliability coefficients range from 0.71 to 0.87[216,257], which are reasonable and more reliable than many other subtests of the WMS-Revised (WMS-R). One-year test-retest reliability has been demonstrated with reliability coefficients of 0.54 and 0.47 [225,258]. In addition, the WMS-R has been extensively validated against the California Verbal Learning Test, showing high correlations[259] [216]. There are some reports of practice effects in repeated administrations of the Logical Memory subtest. [254], but test order does not affect the validity of the Logical Memory test.[260]

Immediate recall of the Logical Memory subtest is reported to remain stable through middle age and then progressively declines. Reports on delayed recall vary, but show decline from age as early as 20 years, with levelling off in the sixth decade, then further decline. However, because age and education are highly correlated in the normative population, it can be difficult to interpret older people's scores as due to age alone. Gender does not appear to be related to score, although education may be. [225]

iii) Other issues

- The WMS, of which the Logical Memory test is part, is among the most commonly employed intelligence tests in adults[261] WMS has been revised in 1987 and 1997/8, the most recent version being called WMS III [218,262,263]
- The Logical Memory subtest measures recognition, recall and learning (with long delayed recall), immediate memory and recent episodic memory,[218] and has frequently been used to assess memory in stroke.
- CAFE adopted the 'items correctly repeated' or 'verbatim' scoring system and used the WMS-R Logical Memory test (LM-R) which has delayed recall at 30mins and has been shown to have consistent interrater reliability. [225,264]
- Limitations of this subtest included lack of adequate scoring criteria and lack of adequate normative information. [261] For example, the time delay for recall varies from 20 minutes to one hour, which is likely to affect the score; however, the revised LMS had improved criteria with a set 30 minute delay. [225]
- Logical memory performance has been shown to be independent of IQ, [216,265] race and gender, [216] although high correlations have been demonstrated between LMS and other tests of learning (and verbal tests, reflecting the need for verbal organisation and syntax in repeating the tests).

d) Digit Span subtest of Wechlser Adult Memory Scale - Revised (WMS-R)

i) Literature on clinical significance or clinical importance

As for the Logical Memory test, the literature search found few reports on clinical significance of performance on the Digit Span test. Again, as for Logical Memory, the digits forwards component of the Digit Span subtest measures memory functions which are equally represented in both

hemispheres, therefore damage to one side of the brain only would have no effect on the performance of this subtest.[266]

Twin studies have demonstrated that the demented twin had shown greater decline on digit forward than the non-demented twin 20 years earlier.[267 225]

This test has been shown to be particularly sensitive to problems with interaction between executive and attentional components, e.g. in HIV,[228] whilst in healthy people, scores on digit span remain good into the 80s, although deterioration in score in this group predicted death within several years. [225,268]

ii) Literature on reliability validity and sensitivity in measuring important differences and change over time

A negative relationship has been demonstrated between initial level of cognitive functioning and rate of change in digit span score. [269] Digit Span has a reported reliability coefficient of 0.88, [216,270] which is considerably higher than many other subtests of the WMS-R.

There are some reports of practice effects in repeated administrations with digit-span [271], although other work reports that these effects, though statistically significant, are negligible. [225] Test order does not affect the validity of Digit Span.[260]

Digits forwards is one of the least sensitive tests to detection of dementia, although scores become noticeably reduced after the early mild stages. [225,272,273] However, prospective work suggests that the Digit Span test (forwards and backwards) is among the neuropsychological measures most sensitive to early changes in cognitive functioning, and is thus best able to delineate normal elderly

subjects from those who later are diagnosed as having probable dementia. Digit Span is also said to be relatively resistant to the effects of normal ageing in contrast to dementia [253], and another prospective study described no significant change in the Digit Span score in a sub-group of the general elderly population who did not go on to develop dementia [252].

Digit Span is part of both the Wechsler Adult Intelligence Scale and the WMS. Both of these scales have been widely used since 1945 [209], and therefore there is much published literature reporting high test and re-test reliability [210] and construct validity [211].

iii) Other issues

- Digit Span is the most common method for measuring span of immediate verbal recall and has a speed component. [225] Digit Span is part of both the WMS[263] and the Wechsler Adult Intelligence Scale (WAIS), which has been very widely used since 1945 [209].
- Digits backwards relies on working memory in addition, and is more of a memory test (involving 'double tracking' since both memory and reversing operations must process simultaneously) than digits forwards. Digit span scores are reduced if there are problems of immediate memory, concentration or attention. [225]
- Because digits forwards measures immediate memory, even patients in advanced stages of dementia could still score highly. Tests which are more unfamiliar, abstract, speed-dependent and need capacity for attention and learning are more likely to be lower in those with progressing dementia (i.e. digits backward, etc).
- Digit span performance correlates highly with intelligence level [216,265].
- The forwards and backwards score is usually combined, with the assumption that the two tests behave similarly. This appears to be the case for those up to around 80 years of age, although some work suggests that as age increases, forward span remains stable but backwards deteriorates. [225,274]

- As recommended in textbooks of neuropsychological assessment, CAFE uses the raw score for digit span, rather than any of the scoring transformations available. [225]
- Education is reported to have an effect on Digit Span score. [225] Age is not reported to have an effect on score below 65/ 70 years. [225,275,276] Anxiety may reduce score [225,277]

e) Rey Complex Figure – copy and delayed recall (also known as the Rey-Osterrieth Complex figure Test)

i) Literature on clinical significance or clinical importance

The Rey Figure can distinguish those with probable Alzheimer's disease from normal. [216,278]

There is evidence to suggest that depression is found to be associated with subtle difficulties in delayed recall. [216,279]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

The literature search revealed few studies of the reliability of change over time of this test.

- Rey copy may not be sensitive to early dementia changes since in dementia, impairments in constructional tests which assess access to semantic and lexical knowledge (e.g. drawing something meaningful) are present early in the disease, whereas impairments in constructional tests that do not need this (e.g. copying Rey figure) are not apparent until later in the dementia.[228] Delayed recall may be more sensitive to memory deficits than immediate recall. For CAFE, as for many other studies, immediate recall was not used, only copy and delayed recall, since there is little difference between copy and immediate recall in normal patients. [216,280,281]

High interrater reliability (>0.90) has been demonstrated for total score (for copy and recall) using the standard scoring system, despite its' subjectivity[282], although more variable interrater reliability has been reported for individual scores on the 18 items. [216,278] There are also reports of a high number of simple scoring errors when using this test, with errors on up to 25% of figures scored[283].

Practice effects of 10% improvement have been demonstrated when retested after one month for the same figure, and a study of elderly patients found the copy was not reliable with retesting at one year, although the delayed recall was moderately reliable at this time interval. [216,278] In addition, a ceiling effect may occur, particularly with copy .[216,284]

Age may affect performance, especially > 70 years, [216,285] perhaps due to age-related deterioration in organisational capacity – the way the person divides the figure into smaller parts,[216,286] and there is consistent evidence of an effect of age on recall, although others find no correlation between score and age for copy. [225]

Only moderate correlation between Rey score and intelligence is reported. [216,280,285] There are conflicting reports on the effect of education on both copy and recall, where some demonstrate poor performance in those with low education, whereas others describe no association. In addition, gender and handedness do not appear to have an effect on Rey score. Rey score is considered sensitive to brain lesions. [216]

iii) Other issues

- The Rey Figure measures planning, organisational skills, problem-solving as well as perceptual, motor and memory factors.[216,284] Rey copy measures visual-constructional ability, delayed recall measures amount retained over time. More precise cognitive functions needed are visual

perception, visuospatial organisation, motor functioning (and memory for recall).[216,286] In addition, Rey score requires use of strategy, for example the best strategy is to deal with the overall figure then the details. [225] It is suggested that this Rey score also measures executive functions (planning/ problem solving), [216,287] and it has been described as a test of incidental learning, [216]a test of visuographic memory and visuographic copying. [225]

- The length of delay between copy and delayed recall varies widely between studies from 3 minutes to 45 minutes, although length of delay does not affect performance if under one hour. [216,278] In the CAFE study, as for others, [207,216] participants were told they would need to recall the figure.
- Analysis of the Rey figure can be in much more detail, for example several methods for observing the patients strategy in copying the figure are reported, although this level of detail in analysis was not performed for CAFE, nor was time taken to copy recorded. [225]
- This test has been reasonably widely used, and the literature reports that although there are often scoring errors with this method [283], scoring can be reliable between scorers[282]. For repeated administrations, some use the Taylor figure (a similar complex figure) for retesting [216,225] in order to reduce possible practice effects (not used for the CAFE study).

f) Paced auditory serial addition test (PASAT)

i) Literature on clinical significance or clinical importance.

The literature search yielded no reports on the clinical significance or importance of scores on the PASAT

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

There is a good evidence for reliability of the PASAT when used in cross-sectional studies,[291,311] although no literature on reliability of change over time. Excellent objectivity through good inter-observer reliability has been demonstrated (r=0.99) for the PASAT[288], but practice effects have been reported .[216,225,289]

There is some evidence for construct validity, with moderate correlations to other measures of attention e.g. digit span, [216] and validity has also been well demonstrated through factor analytic loadings on the attention/ concentration factor.[228]

Reports are conflicting on whether or not there is a correlation with general intelligence [216,290,291] [288]. Some report that there is a correlation with education,[216,292,293] whilst others find no effect of education [216,294] [288] nor gender, although there is an association with age [216,225,294] [291]. However, the PASAT is very sensitive to problems with information processing ability.[225,290]

iii) Other issues

- The PASAT measures information processing capacity similar to that seen on reaction-time and divided attention tasks[228] but also requires good mental arithmetic, verbal ability and complex motor skills. Problems are that it relies on fast speech responses and is not suitable for the very anxious. [216]
- PASAT score has been shown to correlate with NART and WAIS. [216]
- This test is sometimes used to detect malingering, by looking at the pattern of responses. [225]

g) Map search subtest of the Tests of Everyday Attention

i) Literature on clinical significance or clinical importance.

Poor performance indicates a difficulty in ignoring irrelevant information and picking out the targets in complex visual arrays. This may cause problems in reading forms, bus timetables, TV listings and finding items on supermarket shelves etc. [295] 'Poor performance' is determined using comparison with normative values.

As with all of the Tests of Everyday Attention (TEA), Map search has reported ecological validity, i.e. is predictive of everyday functioning. [216,228]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

The literature search yielded no reports of reliability of change over time reliability for Map search.

The tests of the TEA have high reported reliability and ability to discriminate between minimal cognitive decline and mild Alzheimer's disease. Map search test has been shown to have ecological validity and satisfactory reliability,[228] although validity may possibly be affected by visual problems[212]. This test has high test-retest reliability (Pearson's correlation coefficients of 0.83,0.86, 0.87, 0.80), demonstrated for normative populations[212,295].

Score on Map search correlates with other measures of attention, e.g. PASAT, Trails B, and there is no reported correlation with NART IQ. [216]

iii) Other issues

- This test is part of the battery known as 'Tests of Everyday Attention'.[212,295]
- There is a sparsity of other studies/ investigators using the tests of the TEA.[212,213]

h) Telephone search task and i) Telephone search dual task of the Tests of Everyday Attention

i) Literature on clinical significance or clinical importance.

Poor performance on this test indicates difficulty in doing more than one thing at a time, and may lead to problems in, for example, writing a phone message whilst talking to the person leaving the message etc. [295]As with all of the Tests of Everyday Attention (TEA), Telephone search task has reported ecological validity, i.e. is predictive of everyday functioning. [216,228]

ii) Literature on reliability, validity and sensitivity in measuring important differences and change over time

The literature search yielded no reports of reliability of change over time reliability for the Telephone tasks. The Telephone search task is shown to have ecological validity and satisfactory reliability, but although reliability of telephone search while counting (dual task decrement) was satisfactory for two groups of non-brain-damaged subjects (0.51 and 0.61) it was lower in a group of participants with stroke (0.40).[228] The tests of the TEA have high reported reliability and ability to discriminate between minimal cognitive decline and mild Alzheimer's disease, and the Telephone task has demonstrated high test-retest reliability (Pearson's correlation coefficient of 0.61) for normative populations, but is less reliable than other Tests of Everyday Attention with suggested explanations of large and variable learning effects with this test [212,295].

The validity of Telephone tasks may possibly be affected by peripheral auditory deficits[212,295]. However, the Telephone task had been validated using the most inexpensive tape recorder on the market, providing reassurance that high quality equipment was not required, and test validation by the authors had included mild hearing impairment, which did not have an effect on the results.

There is a sparsity of other studies/ investigators using these tests, [212,213] and no studies of reliability of change over time.

iii) Other issues

- This test is part of the battery known as 'Tests of Everyday Attention'.[212,295]
- There is a sparsity of other studies/ investigators using the tests of the TEA [212,213].

Sensitivity Literature

To improve the accuracy of detecting dementia, it is recommended that test results need to be used in combination with analysis of potential confounders, particularly age, sex and education, since insensitivity of neuropsychological tests may produce misleading results. Despite this, tests of episodic memory have been shown to be particularly sensitive in detecting individuals in a preclinical phase of dementia [296].

Most of the literature on test reliability and validity is for assessing/ research in patients with dementia, rather than those with possible mild cognitive decline.

Clinical significance and normative data

When the literature was searched for information on the clinical significance of changes in test scores, it was not possible to find specific criteria on whether or not a score of X or a change of Y over time constitutes a clinically significant score/ change. The literature does suggest, however, that if neuropsychological test scores are compared to age-adjusted norms, a score more than 1 or 1.5 standard deviations (different authors have alternative views on which value is most appropriate) or more below expected level of functioning (using age adjusted means) can be considered as clinically significant cognitive decline such that it meets the neuropsychological assessment component of the criteria for cognitive impairment/ age-associated memory impairment. [219]

Unfortunately, most neuropsychological tests have not been formally standardised, therefore the normative population is usually small numbers of healthy volunteers/ controls. In addition, there are sometimes several sources of normative population data, which may differ, leading to very different results depending on which normative population is selected. Norms for people with limited education do not exist, and norms for very old patients are limited. Therefore it is recommended that raw scores are presented with or without percentile rankings based on norms [261].

It is worth bearing in mind, however, that although neuropsychological tests may not give precise cut-offs for diagnosis of dementia or cognitive impairment, they do provide a reliable baseline for subsequent detection of change. [261]

Comparisons between normative data and the CAFE results are described in chapter 6

Chapter 4 Summary

- The CAFE study neuropsychological test battery was selected because it had developed for the purpose of examining cognitive impairment due to cerebrovascular disease, had been used in the CAFE pilot study, had been validated, was portable and measured a range of cognitive domains (general cognitive function, pre-morbid intelligence, verbal long term memory, short term memory, information processing and attention, selective attention, divided attention and non-verbal memory).
- The tests in the CAFE battery were the Rey Complex Figure, the Mini Mental State Examination, the Logical Memory and Digit Span subtests of the Wechsler Memory Scale (WMS) , the Map Search and Telephone Task subtests of Tests of Everyday Attention, and the Paced Auditory Serial Addition Test. In addition the National Adult Reading Test (NART) was used to measure premorbid intelligence.
- A literature search was undertaken to examine the clinical significance, reliability, sensitivity and validity of performance on the subtests of the CAFE battery. Overall, there was reasonable evidence of reliability and validity of the subtests for use on a cross-sectional basis. However, the literature search revealed very few reports on reliability, sensitivity or validity of the subtests in measuring change over time. In addition, the literature on clinical significance or clinical importance of performance on the subtests was extremely limited.
- Reports on the sensitivity of the tests in detecting dementia were far more plentiful than reports specifically addressing mild cognitive impairment or decline.
- In summary, the CAFE neuropsychological test battery provides an acceptable method of measuring cognitive function in the cohort. Although evidence for reliability and validity of these tests in measuring change over time is limited, this appears to be the case for the majority

of neuropsychological tests. Therefore choice of the tests was made on other grounds, namely the range of cognitive domains tested, and practical factors such as ease of administration, portability and time constraints.

Chapter 5 – Methods

- Part 1: Identification of Participants
    - Practice involvement
    - Form design
    - Notes screening
    - Letter to participants
    - Inclusion and exclusion criteria
    - Power calculation
- Part 2: Interview and Examination
    - Overview of baseline and follow-up visits
    - Details of components included in the visits
    - Validity of interview and examination components
    - Ethical approval
- Chapter Summary

Part 1 - Identification of participants

Recruitment

Practice involvement: Practices were approached by starting with largest practices first. A letter, co-signed by members of the project team (Professor Richard Thomson, Dr Janice O'Connell, Professor Chris Gray and Dr Helen Park), was sent to the senior partner of each practice and I followed this up with a telephone call. At the first visit to the practice, I talked to the senior partner of the practice, and negotiated attendance at a practice meeting, in order to explain the study more fully to all partners. This was to maximise the involvement of all partners in the study, thus maximising the potential number of patients referred to the study. Also during the first visit, the GP checklist (Appendix 5) was completed with the practice manager, and the senior partner signed a consent form (Appendix 6). Posters with details of the CAFÉ study were displayed in surgery waiting rooms of the practices involved (Appendix 7).

Form design: A Microsoft Access form was developed within the project team, in order to make note searching efficient. This led to the production of exclusion and inclusion proformas, in order to collect data on reasons for exclusion at this stage. This would allow identification of possible confounding factors and give an estimate of generalisability of the results to the general population.

Notes screening: We chose to identify patients with atrial fibrillation by performing digoxin searches on GP's computerised patient records (Figure 5.1). This was appropriate and likely to be a representative method of screening since 96% of practices are now computerised. Digoxin screening was thought to be an efficient way of detecting those with AF[297] since 91% of GPs using software use computerised repeat prescribing systems. In addition, screening for those

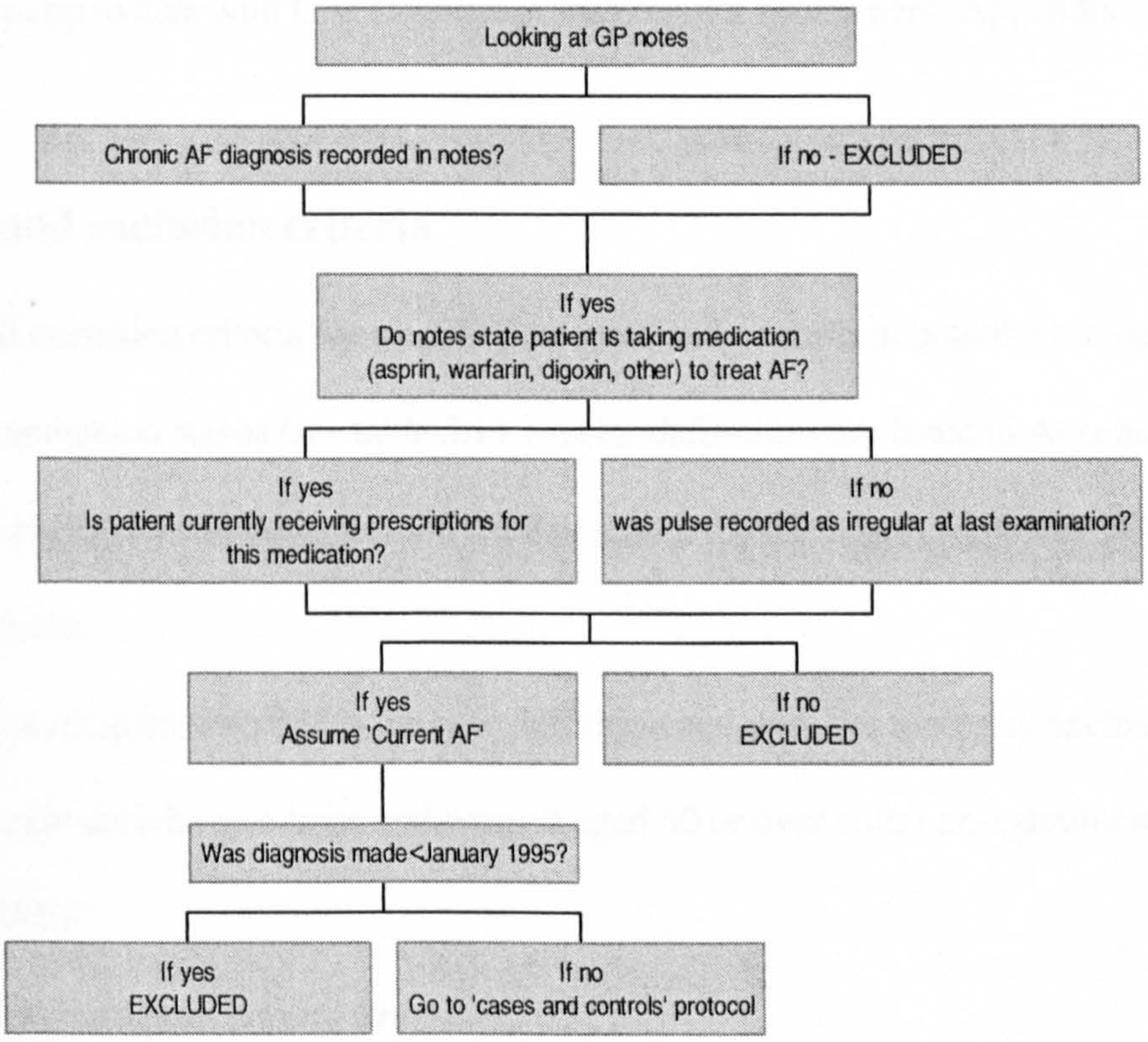
with atrial fibrillation as a problem title Read code was performed wherever problem titles were used by practitioners, but this was less productive, since the extent to which GPs use the computer outwith repeat prescribing is variable. If a practice (n=45) had a computerised disease register for atrial fibrillation then this was run in addition to the digoxin search.

Controls were randomly identified by selecting the adjacent patient on the general practitioner's list when ordered by date of birth and sex (no twins were encountered).

Once notes had been identified in this manner, I hand searched them. At this stage the notes were included or excluded using objective criteria (see below). In either case, relevant details were recorded on the appropriate Access form on a portable computer.

Figure 5.1:

Flowchart for searching GP notes to identify those with atrial fibrillation



Letter to participants

Following identification of potential participants through GPs, patients were invited by letter to participate in the study (see Appendix 7). The letter had been approved by the ethics committee, was signed by the senior partner within the practice, and countersigned by myself. A reply-slip was included for patients to return. All individuals expressing interest in participating also received a patient information leaflet prior to the baseline visit, with full details on precisely what would be involved in the study, again agreed by the ethics committee (Appendix 8). Those participants who did not return a reply-slip received one duplicate of the original invitation letter, in case the first letter had been mislaid. No further follow-up of those who did not reply took place.

GP newsletter

GPs were kept up to date with CAFÉ progress with regular newsletters (Appendix 7).

Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied to cases and controls at both the note searching and interview/examination stages (see table 5.1). Precise definitions are listed in Appendix 9. A checklist for exclusion was designed and used to search the GP notes (Appendix 10).

Inclusion criteria: -

- Any participant who fulfils the case definition and does not meet any exclusion criteria.
- The case definition is 'men and women aged 60 or over with non-valvular atrial fibrillation (NVAF)'.

Reasons for the exclusion criteria are: -

- Established dementia: Several reasons for exclusion of this group include:

1) further cognitive decline would be difficult to assess since the progression of dementia is not constant;

2) completion of the neuropsychological test battery would be extremely difficult with such patients since it requires understanding of the test explanations;

3) these patients may also have other risk factors for dementia, although such potential confounders could be addressed in the analysis;

4) exploration and establishment of cause of dementia would be very difficult in this group since the advantages of a longitudinal study would be of no use in establishing cause of existing dementia at baseline; and

5) CAFÉ aimed to address whether AF is a risk factor for the subsequent development of cognitive decline, rather than addressing whether AF affects further cognitive decline in established dementia.

- Previous stroke/TIA: these patients may have had residual cognitive deficit following their cerebrovascular accident (CVA), making subsequent measurement of cognitive decline difficult. In addition, the CVA may result in problems with vision, language and motor skills that make completion of the neuropsychological test battery difficult.
- Severe visual or hearing impairment: this would affect ability to comply with the test battery.
- Severe congestive heart failure (NYHA class 3 and 4): this is known to increase risk of thromboembolism independently of AF, therefore could bias the results.
- Those who speak English poorly: this would affect understanding of explanations of the test battery, which may lead to underestimate of performance.
- Those who are very frail: this criterion was included to prevent unnecessary intrusion into the lives of those for whom request for help with this research project would be

inappropriate and disturbing, for example the terminally ill. GPs were asked to use their discretion in helping the CAFÉ team to decide who fitted into this group.

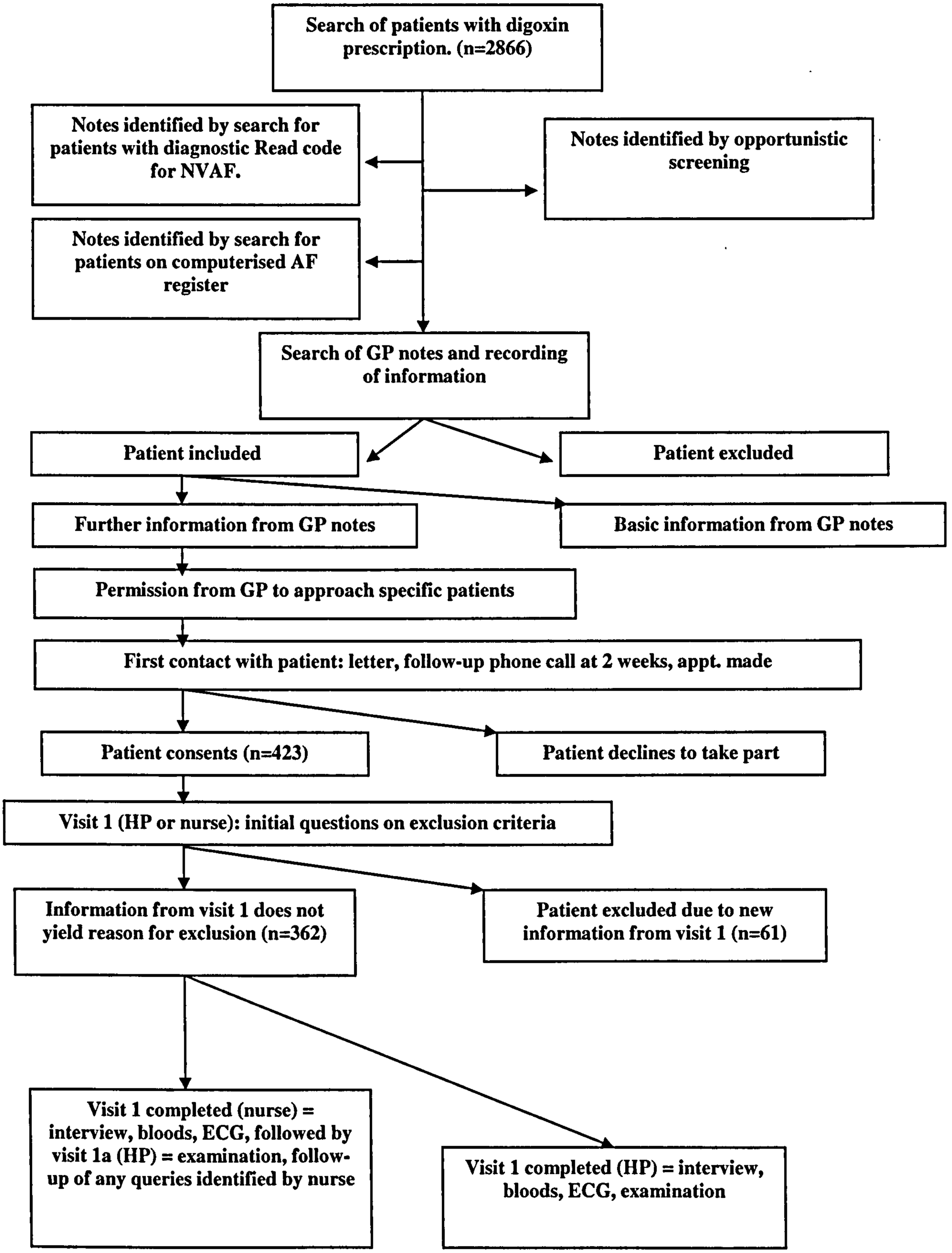
Table 5.1: Summary of CAFÉ exclusion criteria

Exclusion Criterion	How is this ascertained?
Established dementia	From patient record and mini-mental state examination (exclude if <24)
Previous stroke/TIA (WHO criteria)	From patient record + interview + examination
History / clinical findings of rheumatic heart disease	From patient record + examination
Prosthetic valves	From patient record
Severe visual or hearing impairment	From patient record + interview
Cardiac rhythm other than AF or sinus (includes permanent cardiac pace-maker, paroxysmal AF)	From patient record + examination
Severe congestive heart failure (NYHA class 3 and 4)	From patient record + interview
Those who speak English poorly	From interview
Those who are very frail (see definitions)	From patient notes + interview

Power calculation

The sample size provides 80% power to detect a 10% difference in scores on a basket of tests between subgroups. We chose this sample size because a 10% difference is likely to be of clinical importance. Sample size estimation was based on the following calculation, specific to the MMSE: a sample size of 176 (n=352) in each group would have 80% power to detect a difference in means of 1.5 assuming a standard deviation of 5.0 using a two group t-test with a 0.05 two-sided significance level. This sample size would give sufficient power for the detection of clinically meaningful differences for other outcome measures. In addition to focusing on a single outcome variable, a pooled estimate was based on several of the cognitive function tests using the evidence available. This provided a similar sample size to that derived from MMSE.

Figure 5.2: Flowchart to show the process leading to the baseline visit



Part 2 - Interview and Examination

Patients who agreed to participant underwent a baseline visit, carried out in the participant's home by the team doctor alone, or by the nurse and doctor. All participants completed a consent form (Appendix 11). The information collected at baseline included a neuropsychological test battery. In addition data on possible confounders was collected in order to enable these to be incorporated into the analysis. Figure 5.2 depicts the flowchart which was used to plan the baseline visit.

Overview of baseline and follow-up visits

Dataforms used for the visits are provided in Appendix 12.

Baseline visit

The baseline visit included a validated battery of nine neuropsychological tests, as used in the pilot study[15]; a health questionnaire, including information on co-morbidities and contra-indications to anticoagulation; a health status questionnaire (the short-form 36 [298,299]); a physical examination; a limb-lead ECG and a battery of blood tests (detailed later).

Follow-up components

The follow-up visit took place 12 months after the baseline visit. The components of the follow-up visit included a repetition of the validated battery of nine neuropsychological tests, health questionnaire and health status questionnaire.

Details of components included in the visits

1. Neuropsychological test battery

The selection and characteristics of the neuropsychological test battery used in CAFÉ are explored in Chapter 4.

2. Health questionnaire

Participants were taken through a previously validated health questionnaire to collect data on stroke risk factors and contraindications to anticoagulation. [9] This included collection of information on comorbidities, allowing these to be incorporated in the analysis as potential confounders if necessary. These questions had originally been taken from the Health Survey for England[30], and had been validated as part of the Survey's methodological sub-study[30].

3. Health status / quality of life measurement

Measuring quality of life will always be subjective due to the nature of the variable. Definitions for health-related quality of life vary from those which include a holistic emphasis on the social, emotional and physical well-being of a patient to those which focus on the impact of health on the ability to lead a fulfilling life. For the CAFÉ study, health status was measured using the Short Form-36 (SF-36) since this has been widely used internationally and the study team were familiar with it.[298 300]

4. Physical examination

A brief respiratory, cardiovascular and neurological examination was performed, primarily to identify exclusion criteria which may have been missed at the notes-screening stage, for example past stroke or severe heart failure.

5. Blood tests

In order to be able to incorporate potentially confounding variables into the analysis, the following blood tests were carried out: haemoglobin, haematocrit, white blood cells, platelets, urea, creatinine, sodium, potassium, random cholesterol, HbA_{1C}, thyroid function tests, random glucose and digoxin level (for those on digoxin).

6. ECG

The decision was made to carry out limb-lead electrocardiograms (ECGs), which record leads I, II, II, AVR, AVL and AVF. These could be recorded using portable machines, allowing the ECG to be undertaken in the patient's own homes. In addition, the use of limb-leads alone did not necessitate the undressing of patients and was sufficient for confirmation of cardiac rhythm.

Validity of interview and examination components

Development of interview and examination dataforms

Data forms for all components of the baseline interview were piloted and amended accordingly.

Possible sources of bias within interview and examination

The potential for a learning effect was considered when planning the interview and follow-up. Existing work has demonstrated training effects when testing spatial orientation and inductive reasoning [301]. This is a possible source of bias in this study, since there were repeated assessments. However, the duration between visits was 12 months, which makes practice effects less likely than for shorter intervals.

Training of observers

Baseline visits were carried out by two observers (one doctor and one nurse), and participants who were visited by the nurse were also visited by the doctor in order to perform the physical examination. Follow-up visits were carried out by one observer, either the doctor or the nurse. Following piloting of the interview data forms, both observers carried out several (4) visits together before commencing visits alone. At regular intervals throughout the baseline and follow-up visits, the two observers carried out three visits together, to identify any emerging areas of subjectivity and to maintain consistency in the data obtained during the visits.

Blinding

The research nurse was blind to case status whilst undertaking the neuropsychological tests, which were carried out in the first part of the visit. As research doctor, I had originally searched GP records to identify participants, therefore in theory could have known case status, however the large number of records searched (2866) means that this was very unlikely. Observers usually realised case status in the later part of the visit, when questions about health were asked.

Validation of cognitive function tests

Cognitive function tests had already been externally validated, as described earlier. In addition, both observers separately carried out the tests twice (on a healthy volunteer and hospital inpatient) and compared results in order to identify areas of subjectivity.

Validation of blood pressure recording

Blood pressure taking skills were taught in the hospital prior to starting visits. To monitor consistency of blood pressure reading skills and the accuracy of the sphygmomanometer, at regular intervals both observers measured the blood pressure of a third party and compared the readings. Readings were also compared using different sphygmomanometers. During the patient visits, two blood pressure readings were recorded and the British Hypertension Society guidelines for blood pressure measurement were used. [302]

Validation of ECG reading

Training in carrying out portable ECG recordings was undertaken. ECG s carried out by the team nurse were checked by the team doctor.

Validation of medication taken

Medication taken was recorded by the team doctor/ nurse at both visits. Where repeat prescriptions were available, these were used. Where actual medication was available, this was used. This information was compared against the list of current medication obtained when searching GP notes, and any differences were explored further with the patient to identify an accurate record of current medication.

Data cleaning

Data cleaning took place throughout the baseline and follow-up interviews. The databases were designed to minimise entry errors. Examples of data cleaning tasks performed routinely are included in Appendix 13.

Ethical Approval

The study was granted ethical approval by NHS LRECs for Sunderland and South Tyneside. All data was treated as strictly confidential, registered with data protection, and used in accordance with current guidelines.[303]

Missing Data

Due to the rigorous methodological processes used, there was relatively little missing data (searched for as part of data cleaning). Where missing data was discovered, every attempt was made to search for the missing items, by going back to interview forms etc. Where the data was truly missing, an explanation was usually available (e.g. patient became tired, specimen coagulated prior to reaching lab). In these situations data was analysed based on available data only. Particular care was taken with the limited missing data for neuropsychological test scores. When analysing a basket of neuropsychological test scores, all patients who did not have complete data for all test scores were excluded from the analysis (these were very small numbers). When analysing tests individually, all patients with complete data for that test were included in the analysis.

Chapter 5 Summary

- Participants were recruited via general practices. Electronic and paper GP notes were screened using inclusion and exclusion criteria and potential participants were invited by letter to take part in the study.
- Baseline interview consisted of a validated neuropsychological assessment, health questionnaire, assessment of health status, physical examination, limb-lead ECG and blood tests. Follow-up examination at 12 months consisted of the same neuropsychological assessment, health questionnaire and assessment of health status.
- Validation of all components of both interviews was undertaken where possible.
- Ethical approval was obtained for this study from the Sunderland Local Research Ethics Committee and the South Tyneside Local Research Ethics Committee.

Chapter 6 - Results (I): General features of the cohort

- Characteristics of general practices involved
- Stages of exclusion, notes screening and attrition
- Characteristics of responders and non-responders
- Characteristics of the cohort (participants included after baseline interview)
- Normative data for the CAFÉ neuropsychological test battery
- Correlation with National Adult Reading Test scores
- Chapter 6 Summary

Characteristics of general practices involved: -

General practices (n=44) involved in the study were located in Sunderland and South Tyneside in the North East of England. Summary characteristics of these practices are shown in Table 6.1. Characteristics for individual practices are provided in Appendix 14.

Table 6.1. Characteristics of CAFE general practices

GP Characteristic	Descriptive statistics
List size	Mean = 6604 patients Range = 1700 to 14500 patients
Number of partners	Mean = 2.8 whole-time equivalent Range = 1 to 7 whole-time equivalent
Number of practice nurses	Mean = 1.4 full-time equivalent Range = 0.5 to 2.5 full-time equivalent
Anticoagulant service provider (some or all of services)	Secondary care only = 42% Primary care only = 8% Pharmacist-led* = 26% Shared care† = 3% Variety of care‡ = 21%
Level of computerisation of practices	None[a] = 3% Partial[b] = 67% Almost fully[c] = 26% Fully[d] = 5%

*Pharmacist-led clinics, with input from primary or secondary care

†Shared care = organised care shared between primary and secondary care

‡Some patients received primary care, some secondary care

[a]Administration use only

[b]Medication and disease registers

[c]Medication, disease registers and some consultation notes

[d]Paperless

Stages of exclusion, notes screening and attrition:

The stages of recruitment of participants are shown in Figure 5.1. Screening of 2866 sets of GP notes led to 938 (33%) eligible potential participants being invited to interview. Of these, 423 (45%) agreed and were visited at home. Sixty-one (14%) participants were excluded at the baseline interview (47 cases and 14 controls, primarily because exclusion criteria were uncovered during the interview), leaving 362 included participants (175 cases and 187 controls). Reasons for exclusion are outlined in table 6.2(a) (b) (c) and (d).

The attrition rate between the baseline and 12-month follow-up visits was 13.8% for controls and 18.4% for cases.

Table 6.2 (a): Reasons for exclusion – those excluded at notes-screening stage

Reason for exclusion	Number
Aged under 60 years	37
Not currently in chronic atrial fibrillation	370
History of stroke	336
History of transient ischaemic attack	438
Severe heart failure (NYHA class 3 or 4)	12
Severe visual impairment	61
Severe hearing impairment	5
Established dementia	131
Prosthetic valve	80
Pacemaker	33
Rheumatic heart disease	87
Other*	81
Reason not available**	42
Total	**1713**

* other reasons for exclusion included patient terminally ill / too frail /not suitable to participate as advised by the GP

** not available due to failure to collect this information/ failure to record on the database

Table 6.2 (b): Reasons for exclusion – those selected at notes-screening but not invited for interview

Reason for exclusion	Number
Died prior to invitation to participate	26
Not required (recruitment target met)	189
Total	**215**

Table 6.2 (c): Reasons for exclusion – those invited to interview and excluded prior to interview

Reason for exclusion	Number
Refused – various reasons (recorded)	163
Too ill – various illnesses (recorded)	25
Didn't return the form – no reason	278
Other*	49
Total	**515**

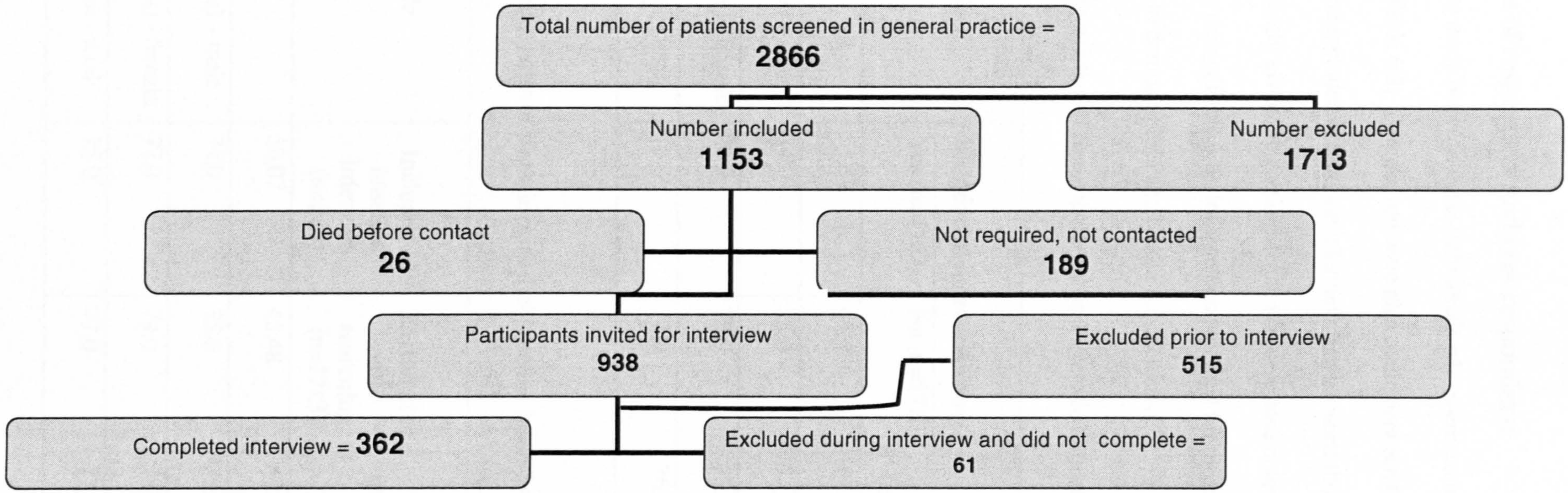
* Includes change of address/ GP

Table 6.2 (d): Reasons for exclusion – those excluded during the baseline interview

Reason for exclusion	Number
History of transient ischaemic attack (missed on notes screening)	6
History of stroke (missed on notes screening)	4
Failed MMSE (<24)	16
Declined to complete interview - various reasons	8
Too ill to complete interview	2
Not in chronic AF	16
Other*	9
Total	**61**

* Includes illiteracy, poor vision and hearing and motivation

Figure 6.1: Flowchart of the screening process



Characteristics of responders and non-responders:

Comparisons were made between those individuals who were excluded and included at the notes-screening stage (Table 6.3). Comparison were also made between those who were excluded at notes screening and included at baseline interview (i.e. between those whose notes were screened and were subsequently invited to participate, and those whose notes were screened and they were not invited to interview) (Table 6.4). Information recorded for those excluded at notes screening stage was limited to demographics and reason for exclusion.

Table 6.3: Characteristics of those included and excluded at notes-screening

Variable	Included at notes-screening?		Total (n=2866)	P-values for comparison of groups
	Yes (n=1153)	No (n=1713)		
Male (%)	51.52	45.48	47.9	P=0.001* (Chi-squared)
Median age (years) – male	74.0	75.0	74.0	P=0.071 (Mann-Whitney)
Median age (years) - female	78.0	79.0	78.0	P=0.007* (Mann-Whitney)
Median age (years) - total	76.0	77.0	76.0	P<0.001* (Mann-Whitney)

*P<0.05

Table 6.4: Characteristics of those included at baseline interview and excluded at notes searching

Variable	Included at baseline interview (n=362)	Excluded at notes searching (n=1713)	Total (n=2075)	P-values for comparison of groups
Male (%)	56.07	45.48	47.33	P<0.001* (Chi-squared)
Median age (years) – male	74.0	75.0	75.0	P=0.177 (Mann-Whitney)
Median age (years) - female	77.0	79.0	78.0	P<0.001* (Mann-Whitney)
Median age (years) - total	75.0	77.0	77.0	P<0.001* (Mann-Whitney)

*P<0.05

In addition, those who were included in the study ('responders', n=362) were compared with those who were invited for interview, yet did not complete the interview ('non-responders', n=576). Comparison between these groups was possible for all variables which had been collected during GP notes screening, with key comparisons described here. The notes screening process had been designed with consideration of the likely need for these analyses.

No significant differences (table 6.5) were found between responders and non-responders for documented co-morbidities (atrial fibrillation, CHF, hypertension, diabetes, thyrotoxicosis, Parkinson's disease, peripheral vascular disease and depression). The only significant differences found were a) female non-responders (median age 79 years) were significantly (p=0.001) older than female responders (median age 77 years), although there was no significant difference in age for men in these two categories; b) significantly (p=0.009) fewer non-responders had a record of CHD (29% of non-responders vs. 37% of responders); and c) significantly (p=0.016) fewer non-responders had ever taken aspirin (39.2% of non-responders versus 47.2% of responders).

Table 6.5: Characteristics of responders and non-responders

Variable	Completed Interview?		Total (n=938)	P-values for comparison of groups (2sf)
	Yes (n=362)	No (n=576)		
Median age (years) – male	74.0	75.0	75.0	0.13 (Mann-Whitney)
Median age (years) - female	77.0	79.0	76.0	0.00* (Mann-Whitney)
Median age (years) - total	75.0	77.0	76.0	0.00* (Mann-Whitney)
Coronary Heart Disease	37.0%	28.8%	32.0%	0.009* (Chi-squared)
Heart Failure	6.6%	6.3%	6.4%	0.82 (Chi-squared)
Hypertension	38.4%	35.1%	36.4%	0.31 (Chi-squared)
Diabetes	10.2%	9.4%	9.7%	0.67 (Chi-squared)
Thyrotoxicosis	1.9%	1.2%	1.5%	0.38 (Chi-squared)
Parkinson's Disease	0.6%	1.2%	1.0%	0.31 (Chi-squared)
Peripheral Vascular Disease	7.7%	5.3%	6.2%	(0.17) (Chi-squared)
Depression (past history)	10.2%	9.7%	9.9%	0.80 (Chi-squared)
Depression (current)	2.8%	3.0%	2.9%	0.86 (Chi-squared)
Case status of those invited to participate – cases/ controls	48.1% /51.9%	50.7% /49.3%	49.7% /50.3%	0.43 (Chi-squared)
Ever taken aspirin	47.2%	39.2%	42.3%	0.016* (Chi-squared)
Ever taken warfarin	24.6%	20.3%	22.0%	0.12 (Chi-squared)

Characteristics of the cohort (participants included after baseline interview):

General characteristics of the cohort

The median age of the CAFE cohort (those who were included following baseline assessment) was 75 years; 56% were male, 37% had a record of CHD, 6.6% had CHF (NYHA grade I or II); 38.4% had a record of hypertension and 10.2% had a record of diabetes. Further characteristics are shown in table 6.6 below.

Comparison of cases and controls

Controls and cases were comparable in most respects. Significant differences between cases and controls are listed in table 6.6. In addition, cases had significantly poorer scores than controls on all analysed components of the SF-36 ($p<0.01$ to $p<0.001$), except for the pain component, where the poorer score in cases was non-significant ($p=0.1$). With regard to treatment subgroups, 51% of cases and no controls were on warfarin at the time of the baseline interview, 35% of cases and 30% of controls were on aspirin, and 14% of cases and 70% of controls were on neither aspirin nor warfarin.

There were no significant ($p<0.05$) differences between cases and controls for the following variables: -

- Age and sex: cases and controls had a mean age of 75.4 years and 75.6 years respectively. 54.9% of cases and 57% of controls were male.
- Duration of NVAF (cases only): mean duration was 417 days (standard deviation 561.57 days).
- Prevalence of hypertension: 42.6% of cases and 35.2% of controls had a GP record of hypertension.
- Prevalence of peripheral vascular disease: 6.8% of cases and 7.1% of controls.

- Oedema on examination: 12.6% of cases and 7.0% of controls had oedema on examination at the baseline interview.
- Smoking status: 13.1% of cases and 15.1% of controls were smokers.
- Alcohol consumption: 17.7% of cases and 22.6% of controls were daily drinkers.
- Level of education: cases and controls were similar with respect both to age at leaving school and highest qualification: 62.3% of cases and 68.3% of controls left higher education at 14 years old or younger; 73.1% of cases and 67.7% of controls had no qualifications (not including apprenticeship).

Table 6.6. Characteristics of the cohort which were significantly different for cases and controls

Characteristic		Mean			p-value
		Total Study Population	Cases	Controls	
Record of diabetes (%)		10.2	16	4.4	P=0.001
HBA1C		6.2	6.7	5.9	P<0.001
Cholesterol		5.6	5.3	5.8	P<0.001
Record of coronary heart disease (%)		37.0	44.4	31.9	P=0.017
Congestive heart failure	History of swollen ankles (%)	30.8	42.9	19.4	P<0.001
	History of marked shortness of breath (%)	6.4	8.0	5.4	P<0.001
	Record of recent symptomatic heart failure (%)	6.7	11.8	1.1	P<0.001

Statistically significant differences between the two groups are discussed further under 'potential confounders' later and have been taken into account in subsequent analyses.

Normative data for the CAFE neuropsychological test battery

Normative data for tests of the CAFE battery was available for neuropsychological performance at an isolated point in time, rather than change in performance over time, and for some tests there was no normative data available at all. Therefore comparisons between CAFE data and normative data could only be made on a cross-sectional basis (CAFE baseline data was used for the following comparisons).

1) Wechsler Memory Scale norms

i) Logical Memory

The Logical Memory Scale normative population was originally small and young (approximately 200 people, aged 20-50 years),[216,225] although this was extended to 360 in age groups 16 to 74 for the revised version.[218] Therefore CAFE used normative data from a selection of later studies to obtain reference values for older age groups as shown in table 4.1. The overall mean immediate score (A+B/ 2) for the total CAFÉ population was 7.30 (SD 2.97), which is consistent with what would be expected considering the norms listed in table 6.7.

Table 6.7: Normative data for the logical memory subtest of Wechsler's memory scale

Age group (years)	Score for normative population[225]									
	Abikoff[256]		Hulicka[304]		Haaland[305]		Larrabee[306]		Klonoff[307]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
55-64	-	-	-	-	-	-	-	-	-	-
60-69	-	-	7.34	2.9	-	-	9.1	2.6	-	-
65-69	-	-	-	-	7.4	2.5	-	-	-	-
70-74	-	-	-	-	6.7	2.6	-	-	-	-
70-79	9.11/ 11.83	-	7.4	3.8	-	-	8.5	2.4	-	-
75-79		-	-	-	5.9	2.5	-	-	-	-
80-92		-	-	-	-	-	-	-	5.7	2.9

ii) Digit Span

The normal range for digits forwards is 6 +/- 1, [225,308,309] with a score of 5 reported as within marginal limits, 4 as borderline and 3 as defective. For digits backwards, raw scores of 4 to 5 are reported as normal, 3 as borderline defective or defective, depending on educational background and 2 as defective for everyone. The average reported total raw score for this test is 13 in the 70-74 age group. [225] CAFE results are consistent with this, with a mean raw score of 13.8 for the whole study sample. [225,310] Sufficient data was not available to make comparisons between the CAFE cohort and the normative population for key characteristics.

2) Tests of Everyday Attention (Map Search and Telephone Task) norms

Normative population

The normative population used for the Tests of Everyday Attention was a sample of 154 normal volunteers, aged between 18 and 80 years, of whom 43 volunteers were in the age-band relevant to CAFÉ (65- 80 years). CAFÉ was comparable to this population in that (236/361) 65.4% of the CAFÉ cohort had an IQ of 100 or greater, in comparison to 74% of the normative population. The CAFÉ cohort had a greater age range (60 to 90 years at first interview). In the CAFÉ cohort, (201/361) 55.7% were male, compared to 45% of the normative population. Comparisons with the normative population, recommended by the authors of the test (as were performed for the CAFÉ cohort) are made by transforming the raw scores using an approximately normal power transformation to obtain a scaled score and percentile.

The map search tests are transformed to a scaled score using tables with adjustment for age, and these transformed scores are then converted to percentiles based on a normative population. For the CAFÉ cohort, percentiles are shown in table 6.8, and are interpreted as in the following example:

Map Search (1st Minute, Left) percentile = 43.4%, implying that the CAFÉ cohort scored better than 43.4% of the normative population in their age-group. Reasons for the relatively poor performance in the Map Search and Telephone task subtests may be because the CAFÉ cohort is older and more frail than the normative population.

Table 6.8: Percentiles for CAFÉ cohort (from normative population)

Neuropsychological test battery	CAFÉ mean score (whole study population)	Scaled score equivalent of raw score	Percentile range (from normative population in this age range) (%)
Map Search (1 Minute, Left+Right)	15.59 + 5.05 = 20.64	9	30.9-43.4
Map Search (2 Minutes Left+Right)	20.64+9.20+8.75 =38.59	7	12.2-20.2
Telephone Task (time per target)	6.5085 (SD=13.84)	6	6.7-12.2
Telephone Task (dual task decrement)	4.136 (SD=14.48)	7	12.2-20.2

3) *PASAT norms*

Limited norms are available for the PASAT and are presented as total scores only. This makes comparison with CAFÉ sub-scores difficult, since for CAFÉ, as with many other studies, only two of the four speeds available were used.[311] Other available norms were of much younger age-groups (mean age29.2 years) than the CAFÉ cohort, again making comparison very difficult.[291] The only available norms of an older age-group (60 to 75 years) demonstrated considerably higher scores than the CAFÉ cohort (mean raw score of 37 for PASAT-2.4 and 20 for PASAT-1.2 for the normative population, compared to 29 and 12 for the CAFÉ cohort). This may be explained by the

fact that the normative population were younger than the CAFÉ cohort, and in addition the normative sample in this age-group was very small (n=61).[312]

4) NART norms

Norms for a adapted version of the NART, the NAART,[216,313] have been reported as follows:- age 60-69 years (n=29), mean number correct = 43.06, SD =10.78; age 70+ (n=31), mean number correct= 45.81 (SD= 8.43). The CAFE cohort scored considerably worse than the normative population on this test, with mean of 28 words correct for the whole study sample. Reasons for the difference between CAFE findings and the normative population are difficult to establish due to the lack of information available on key characteristics of the normative population, although differences in educational level are a possible explanation.

5) MMSE norms

The lowest quartile cut-off for this test is a score of 28 for those aged 50-79 years and 26 for 80-89 year olds. [225,314] CAFE data fits well with this, with a lowest quartile score of 27.0. Norms have also been reported according to educational level. [216]

6) Rey norms

Several normative populations are reported for this test[218]:-

- One normative population was 18-89 years, healthy and well-educated.[216,284,315] These norms are for those with no immediate recall, only copy and 30 minute delayed recall (as was used for CAFE): Age 60-69 years (n=21): Copy mean= 30.79 (SD=4.21); 30 min

recall mean = 14.21 (SD=7.50). Age 70+ years(n=23): Copy mean= 29.57 (SD=3.37); 30 min recall mean = 11.74 (SD=6.11).

- Others report that mean *copy* scores do not differ between age groups, with a mean score of 33.90 (SD 2.4) for those aged 65 years plus,[225,316] and a mean of 32.90 (SD 2.7) for those aged 70 + years. [216,225]
- CAFE findings compare well with both of these normative populations, with a mean copy score of 31.75 and a mean delayed score of 13.2 for the whole study sample.

Correlation with National Adult Reading Test Scores:

As part of a factor analysis, the relationship between performance on different tests was examined. Of particular interest was the relationship between NART IQ and the other tests, since NART IQ is a recognised marker for verbal intelligence which may have an effect on cognitive performance.

For the CAFE cohort, there was little correlation between NART IQ and performance on other tests in the CAFÉ battery (table 6.9) at baseline, suggesting that the CAFE findings are not affected by the verbal intelligence level of individuals in the cohort. This contrasts with other test batteries, such as the complete WAIS, which has been shown to correlate with education.[218]

Table 6.9: Correlation (Spearman's) between NART IQ and performance on other neuropsychological tests: -

Neuropsychological Test	Spearman's correlation (2dp)	P-value for Spearman's correlation (2dp)
MMSE	0.39	0.00
Logical Memory Immediate (raw)	0.34	0.00
Logical Memory Immediate (%)	0.33	0.00
Logical Memory Delayed (raw)*	0.29	0.00
Logical Memory Delayed (%)	0.29	0.00
Rey Complex Figure Copy*	0.22	0.00
Rey Complex Figure Delayed	0.23	0.00
Map Search (1st Minute, Left)	0.16	0.002
Map Search (1st Minute, Right)	-0.07	0.20
Map Search (2nd Minute, Left	-0.01	0.81
Map Search (2nd Minute, Right)	0.10	0.05
Telephone Task No. of Targets*	0.04	0.23
Telephone Task Time Taken (seconds) *	-0.07	0.17
Telephone Task Dual Task Decrement	-0.20	0.00
NART No. of Errors	-0.98	0.00
NART Predicted IQ	1.00	-
Digit Span	0.49	0.00
PASAT (2.4-seconds)	0.24	0.00
PASAT (1.2-seconds)	0.09	0.09

Chapter summary

- Participants were recruited from general practices in Sunderland and South Tyneside, which ranged from large practices with list sizes of 14,500 patients to small, single-handed practices.
- 43% of notes screened were included as potential participants, with the major reasons for exclusion at this stage being history of stroke/TIA or person not in chronic NVAF.
- Stages of recruitment involved applying exclusion criteria during screening of notes in general practice and at baseline interview. A large proportion (55%) of potential participants declined to take part after invitation, and a smaller proportion (14%) were excluded at interview.
- Female responders were slightly younger than female non-responders (median 77 versus 79 years) and responders were more likely to have a record of CHD and to have taken aspirin than non-responders. There were no significant differences between responders and non-responders for other characteristics or documented co-morbidities (atrial fibrillation, CHF, hypertension, diabetes, thyrotoxicosis, Parkinson's disease, peripheral vascular disease and depression).
- The median age of the CAFE cohort was 75 years; 56% were male, 37% had a record of CHD, 6.6% had CHF; 38.4% had a record of hypertension and 10.2% had a record of diabetes.
- Characteristics of the cohort were examined with comparison of cases and controls. There were significant differences between cases and controls for measures of diabetes, cholesterol level, CHD, CHF and SF-36 score. These key variables were noted for incorporation into subsequent analysis of potential confounders (see chapter 7).

- CAFE baseline data compared well with normative data available on Logical Memory, Digit Span, MMSE and Rey Complex figure. However, for the NART and the Tests of Everyday Attention the CAFE cohort scored worse than the normative population.

- There was little correlation between NART IQ and performance on other tests in the CAFÉ battery at baseline; therefore it was unlikely that verbal intelligence would confound the findings.

Chapter 7 - Results (II): Baseline Results - Neuropsychological test battery scores

- Statistical Methods
- Findings of neuropsychological test results at baseline:
    - Comparison between cases and controls
    - Comparison of sub-groups
    - Summary of neuropsychological test results at baseline
- Examination of potential confounders:
    - For the total population
    - For cases versus controls
    - For subgroups
- Stratification according to stroke risk
- Chapter 7 Summary

Statistical Methods

Where appropriate we have used means, with use of medians when distributions were non-normal. Analysis of variance (ANOVA) models were used for all parametric data and, where appropriate, variables were entered into the model as covariates in order to address confounding. Where the data were non-normal, equivalent non-parametric methods were applied. Spearman's rank correlation coefficient (rho) or Pearson's product moment coefficient (p) were used to explore associations between variables. For two-group analyses Student's t-test was used to compare differences between means and where there were more than two groups, one-way ANOVA was applied with a Bonferroni correction where appropriate. As much of the data were non-normal, tests such as the Mann-Whitney test for independent samples were applied. Individual components of the neuropsychological test battery were analysed separately.

For the section on stratification according to stroke risk, cases only were categorised as high, intermediate or low stroke risk according to SPAF criteria[55,58,69] as described in Chapter 2. Firstly descriptive characteristics were calculated to determine the proportion of participants in each group. One-way ANOVA, and post-hoc tests were then used to compare baseline neuropsychological test scores between those of different stroke risks.

Matching

Matching by age/sex/practice was not initiated for the purpose of matched pair analysis, but to ensure that we had parity of groups such that the groups were comparable for major potential confounders.

Findings of neuropsychological test results at baseline:

Comparison of cases and controls

a) Crude comparisons

Mean values for performance on all cognitive function tests for the whole study population were calculated (Table 7.1). Performance of cases and controls on all sub-tests was then compared using Student's t-tests. There were no significant differences between means for cases and controls except for one sub-test, 'telephone task time taken' (p=0.001).

Table 7.1: Mean cognitive function test scores for cases and controls (unadjusted)

Neuropsychological Test	Cases (score) (2dp)			Controls (score) (2dp)		
	Mean	Median	SD	Mean score	Median	SD
MMSE	28.4	29.0	1.68	28.45	29.00	1.60
Logical Memory Immediate (%)	25.73	18.00	23.62	24.57	17.00	23.28
Logical Memory Delayed (%)	37.75	36.00	25.76	36.51	36.00	24.43
Rey Complex Figure Copy	31.82	33.00	4.68	31.68	34.00	5.07
Rey Complex Figure Delayed	12.41	12.00	6.36	13.54	13.00	6.95
Map Search (1st Minute, Left)	15.59	16.00	8.30	17.76	18.00	9.67
Map Search (1st Minute, Right)	5.05	0.00	7.24	5.24	1.00	7.26
Map Search (2nd Minute, Left	9.20	9.00	6.67	9.47	8.00	7.96
Map Search (2nd Minute, Right)	8.75	7.00	8.21	10.01	8.00	9.22
Telephone Task No. of Targets	17.44	18.00	3.29	07.73	18.00	4.18
Telephone Task Time Taken	105.37	95.00	46.16	92.71	84.00	36.10
Telephone Task Dual Task Decrement	5.32	2.35	21.31	3.33	2.20	4.25
NART No. of Errors	22.17	22.00	10.35	21.75	21.00	9.88
NART Predicted IQ	103.28	103.00	12.91	103.59	105.00	12.23
Digit Span	13.85	14.00	3.59	13.78	13.00	3.89
PASAT (2.4-seconds)	29.38	29.00	15.98	28.93	29.00	18.30
PASAT (1.2-seconds)	11.86	7.50	12.33	12.37	8.00	13.50

b) Age-adjusted comparisons

The results of the cognitive function tests were then adjusted for age using analysis of covariates (ANCOVA) techniques with age introduced as a covariate (table 7.2).

Adjustment was made for age only at this stage following testing with a multivariate model (ANCOVA): all key confounders were incorporated into the multivariate model comparing cognitive function in cases with controls, with confounders as covariates. There was almost no effect of confounders on the neuropsychological tests for both cases and controls, with only age showing borderline significance. Therefore the following analyses were adjusted for age only.

After adjustment for age only, apart from for one item, the results were again not significant at the 5% level; for 'time taken to perform the telephone task' cases took a significantly longer time to complete than controls (P=0.004) (104.2 seconds for cases versus 92.9 seconds for controls). The difference between mean test scores for case and controls was of borderline significance for a further two sub-tests, the Rey complex copy (p=0.098) and Map 1 minute left (p=0.061).

Table 7.2: Age-adjusted ANCOVA for the mean difference in test score between cases and controls.

Neuropsychological Test	Mean score (Std. Dev.) Case	Mean score (Std. Dev.) Control	Mean difference in score Case-Control	P-value (if borderline or significant) or N/S = not significant
MMSE	28.4 (1.6)	28.5 (1.6)	-0.01	N/S
Logical Memory Immediate	14.3 (5.9)	15.0 (6.0)	-0.70	N/S
Logical Memory Delayed	10.8 (6.8)	10.9 (6.4)	-0.10	N/S
Rey complex figure Copy	31.9 (4.5)	31.9 (4.8)	0.00	N/S
Rey complex figure Delayed	12.5 (6.5)	13.6 (7.0)	-1.10	0.078
Map search (1 minute left)	15.9 (8.4)	17.5 (9.4)	-1.60	0.061
Map search (1 minute right)	5.0 (7.1)	5.5 (7.6)	-0.50	N/S
Map search (2 minutes left)	9.2 (7.2)	10.0 (7.9)	-0.80	N/S
Map search (2 minutes right)	8.8 (8.1)	9.7 (8.9)	-0.90	N/S
Telephone Task: No of Targets	17.4 (3.3)	17.7 (2.7)	-0.30	N/S
Telephone Task: Time Taken	104.2 (43.9)	92.9 (35.0)	11.30	0.004
Telephone Task: Dual Task Decrement	5.5 (20.5)	2.9 (3.8)	2.60	N/S
NART, No Errors	22.0 (10.2)	21.4 (9.9)	0.60	N/S
NART, Predicted IQ	103.5 (12.8)	103.5 (13.8)	0.00	N/S
PASAT (2.4-seconds)	29.6 (16.1)	30.1 (18.1)	-0.50	N/S
PASAT (1.2-seconds)	12.0 (12.3)	12.7 (13.3)	-0.70	N/S
Digit Span	13.5 (3.6)	13.8 (3.7)	-0.30	N/S

*p=0.001 (Bonferroni correction)

From these results, the overall effect of NVAF on cognitive function at baseline is minimal.

Analysis of subgroups according to antithrombotic therapy

a) Crude comparisons

In addition to comparing cases and controls, we used ANOVA techniques to compare subgroups of cases who were taking (a) warfarin, (b) aspirin, (c) neither treatment; and controls who were taking either (d) aspirin or (e) neither treatment (no controls were taking warfarin). The means are shown in table 7.3. Multiple comparison techniques were used to determine whether differences between subgroup means were statistically significant. When the crude data was analysed, there was a significant difference between the subgroups for five subtests (logical memory delayed raw, Rey copy, telephone task no. of targets, tele time taken, digit span). The multiple comparison analyses for these significant between-subgroup differences are shown in table 7.4.

Table 7.3: Mean cognitive function test scores for treatment subgroups (unadjusted)

Neuropsychological Test	Mean Score (SD) (2dp)				
	Cases			Controls	
	Aspirin	Warfarin	Neither	Aspirin	Neither
MMSE	28.36 (1.58)	28.64 (1.53)	27.92 (2.00)	28.07 (1.81)	28.57 (1.53)
Logical Memory Immediate (raw)	12.98 (5.43)	15.54 (6.14)	12.80 (5.26)	14.29 (5.77)	15.21 (6.13)
Logical Memory Immediate (%)	20.10 (19.64)	28.61 (25.55)	19.60 (17.67)	24.27 (22.76)	26.50 (24.46)
Logical Memory Delayed (raw)*	8.90 (5.69)	12.44 (7.22)	9.08 (5.91)	9.87 (6.20)	11.33 (6.50)
Logical Memory Delayed (%)	31.21 (22.09)	40.34 (27.05)	32.40 (22.41)	34.13 (22.93)	35.57 (24.93)
Rey Complex Figure Copy*	30.46 (5.94)	33.07 (3.25)	30.20 (4.26)	32.18 (4.86)	31.81 (4.86)
Rey Complex Figure Delayed	11.256 (6.58)	13.84 (6.30)	10.30 (6.01)	13.16 (7.54)	13.81 (6.81)
Map Search (1st Minute, Left)	15.54 (8.35)	16.66 (8.38)	13.48 (7.76)	18.13 (9.88)	17.16 (9.31)
Map Search (1st Minute, Right)	4.03 (6.41)	5.33 (7.41)	6.24 (7.88)	4.29 (7.78)	5.98 (7.57)
Map Search (2nd Minute, Left	8.38 (6.38)	9.51 (6.58)	9.20 (9.04)	9.51 (7.86)	10.06 (7.97)
Map Search (2nd Minute, Right)	8.20 (7.63)	9.08 (8.46)	8.36 (8.22)	10.38 (8.81)	9.43 (9.06)
Telephone Task No. of Targets*	16.47 (4.06)	18.11 (2.36)	17.24 (3.35)	17.27 (3.47)	17.80 (2.23)
Telephone Task Time Taken (seconds) *	118.43 (58.12)	92.97 (29.50)	111.68 (36.00)	90.25 (26.20)	94.23 (38.31)
Telephone Task Dual Task Decrement	7.90 (31.79)	3.26 (7.04)	7.46 (18.64)	2.29 (3.61)	3.245 (3.86)
NART No. of Errors	22.39 (10.05)	20.87 (9.92)	21.12 (10.85)	22.89 (10.08)	20.74 (9.80)
NART Predicted IQ	102.98 (12.57)	104.89 (12.35)	99.64 (13.46)	100.72 (15.93)	104.73 (12.81)
Digit Span *	13.13 (3.65)	14.26 (3.58)	11.72 (2.56)	13.82 (2.94)	13.73 (4.00)
PASAT (2.4-seconds)	29.18 (15.84)	32.37 (15.27)	20.12 (16.00)	31.78 (18.79)	29.22 (17.83)
PASAT (1.2-seconds)	13.16 (13.07)	12.64 (11.91)	6.88 (10.32)	14.56 (13.57)	12.26 (13.27)

* Significant difference between groups ($p \leq 0.05$)

Table 7.4: Multiple comparisons of cognitive function test scores for treatment subgroups (unadjusted) (only shown for those tests that had a significant difference between groups)

Neuropsychological Test		p-value (where p≤ 0.05)				
		Cases			Controls	
		Aspirin	Warfarin	Neither	Aspirin	Neither
Logical Memory Delayed (raw)	Asp Case	-	0.024	ns	ns	ns
	Warf Case	0.024	-	ns	ns	ns
	Neith Case	ns	ns	-	ns	ns
	Asp Contr	ns	ns	ns	-	ns
	Neith Cont	ns	ns	ns	ns	-
Rey Complex Figure Copy	Asp Case	-	0.015	ns	ns	ns
	Warf Case	0.015	-	ns	ns	ns
	Neith Case	ns	ns	-	ns	ns
	Asp Contr	ns	ns	ns	-	ns
	Neith Cont	ns	ns	ns	ns	-
Telephone Task No. of Targets	Asp Case	-	0.008	0.033	ns	ns
	Warf Case	0.008	-	ns	ns	ns
	Neith Case	ns	ns	-	ns	ns
	Asp Contr	ns	ns	ns	-	ns
	Neith Cont	0.033	ns	ns	ns	-
Telephone Task Time Taken (seconds)	Asp Case	-	0.00	0.00	0.00	ns
	Warf Case	0.00	-	ns	ns	ns
	Neith Case	ns	ns	-	ns	ns
	Asp Contr	ns	ns	ns	-	ns
	Neith Cont	ns	ns	ns	ns	-
Digit Span *(p=0.05)	Asp Case	-	ns	ns	ns	ns
	Warf Case	ns	-	0.05	ns	ns
	Neith Case	ns	0.05	-	ns	ns
	Asp Contr	ns	ns	ns	-	ns
	Neith Cont	ns	ns	ns	ns	-

ns = not significant (p≥0.05)

b) Age-adjusted comparisons

The differences in mean test scores between the groups were then analysed using ANOVA with adjustment for age and Bonferroni correction where appropriate. Again, multiple comparison techniques were used to analyse whether or not differences in means between subgroups were statistically significant. Table 7.5 shows the mean differences with adjustment for age using ANOVA on those cognitive function tests that were significant without age as a covariate. There

were no significant differences between test mean scores for all but one of the subtests. Only the statistically significant result for 'telephone task time taken' persisted, with aspirin cases performing significantly worse than aspirin controls (p=0.004). In addition, a previously non-significant result for this sub-test became significant, with aspirin cases now performing significantly worse than controls on neither aspirin nor warfarin (p=0.011). The multiple comparison analyses for these significant between-subgroup differences are shown in table 7.6. The other significant differences demonstrated with crude analysis of the data disappeared with adjustment for age.

These findings suggest that the statistically significant difference between mean scores for cases and controls found for the 'telephone task time taken' sub-test is predominantly due to the statistically significant difference between mean scores for aspirin cases and aspirin controls/ controls on neither aspirin nor warfarin.

Table 7.5: Mean cognitive function test scores for treatment subgroups with adjustment for age (as a covariate)

Neuropsychological Test	Mean Score (SD)				
	Cases			Controls	
	Aspirin	Warfarin	Neither	Aspirin	Neither
Logical Memory Delayed (raw) [b]	9.71	11.63	9.85	10.06	11.27
Rey Complex Figure Copy [b]	30.86	32.66	30.58	32.28	31.78
Telephone Task No. of Targets [b]	16.71	17.87	17.48	17.36	17.78
Telephone Task Time Taken (seconds)* [p]	114.42	96.99	107.68	89.20	94.56
Digit Span [b]	13.21	14.18	11.8	13.84	13.73

* Significant difference between groups ($p \leq 0.05$)

[b] A higher score represents better cognitive function

[p] A higher score represents poorer cognitive function

Table 7.6: Multiple comparisons of cognitive function test scores for treatment subgroups (adjusted for age) (only shown for those tests that had a significant difference between groups)

Neuropsychological Test		p-value (where p≤ 0.05)				
		Cases			Controls	
		Aspirin	Warfarin	Neither	Aspirin	Neither
Telephone Task Time Taken (seconds)	Asp Case	-	ns	ns	0.004	0.011
	Warf Case	ns	-	ns	ns	Ns
	Neith Case	ns	ns	-	ns	Ns
	Asp Contr	0.004	ns	ns	-	Ns
	Neith Cont	0.011	ns	ns	ns	-

ns = not significant (p ≥ 0.05)

Summary of findings of neuropsychological test results at baseline

There were no significant differences in cognitive function at baseline between cases and controls, nor between subgroups on aspirin, warfarin or neither treatment for the majority of sub-tests. This conclusion was drawn from analyses adjusted for age, and suggests that the effect of NVAF on performance of this battery of neuropsychological tests at baseline is minimal, regardless of antithrombotic treatment.

Examination of potential confounders

Choice of variables

It was important to address the possibility of potential confounders affecting the results, since it was possible that these factors may produce falsely positive findings, or alternatively hide true positive findings. The choice of which potential confounders to incorporate into the analysis was based on an extensive literature search of factors that may affect cognitive decline. These included age, duration of AF, coronary heart disease (CHD), diabetes, hypertension, cholesterol, health status (SF-36), CHF and education. For the purposes of the analyses reported here, sources of data for potentially confounding variables identified are shown in table 7.7.

Table 7.7 Sources of data for potentially confounding variables, for the purposes of analyses described in this section.

Potentially confounding variable	**Source of data for this analysis**
Age	GP notes and interview
Duration of AF	GP notes :- *'date of diagnosis of AF'*
Coronary Heart Disease (CHD)	GP notes:- – *'any record of CHD?'* – *'if CHD, is there a record of myocardial infarction?'* – *'if CHD , is there a record of angina?'*
Diabetes	GP notes:- *'any record of diabetes?'*
Hypertension	GP notes:- *'is patient taking medication for hypertension'*
Cholesterol	Blood sample taken at interview
Health status	SF-36 findings at interview
Heart Failure	GP notes:-*'any record of symptomatic heart failure in the last three months?'*
Education	Interview:- – *'how old were you when you left continuous full-time education?'* – *'highest qualification'*

In order to find out whether any of these factors were likely to confound the analyses, the effect of these variables on the cognitive function test results was investigated in several stages:-

- Assessment of key confounders in the population as a whole.
- Assessment of key confounders as covariates to investigate their effect on the relationship between case status and cognitive function.
- Assessment of key confounders as covariates to investigate their effect on the relationship between treatment subgroups (aspirin/ warfarin/ neither) and cognitive function.

1. Assessment of key confounders in the population as a whole

Initially it was important to determine whether, within our population, there was any association between potential confounders and the results of the cognitive function tests. To do this, initially one-way analysis of variance techniques (usually Student's t-test) were carried out to examine their relationship with each of the neuropsychological tests. In these analyses, the neuropsychological tests were the 'dependant variables' and the potential confounders were the 'factors'. However, it became apparent that the data was non-normal, therefore it was necessary to use non-parametric tests for further analysis. Each potentially confounding variable was then taken in turn and Mann Whitney tests for categorical variables and correlations (Spearman's, Pearson's or both) for continuous variables were then carried out. This led to the following findings:-

a) Effect of coronary heart disease on the neuropsychological test results of the whole population (Table 7.8)

Overall, the proxies for CHD did not produce a significant effect on any of the neuropsychological variables. Statistically significant differences between those with and without proxies for CHD (history of CHD, history of MI, history of angina) were shown for the MMSE. However, looking more closely, both the medians (29.00 for those with CHD, 29.00 for those without CHD) and means (28.16 for those with CHD, 28.60 for those without CHD) were very similar for those with and without CHD, such that the clinical significance of the difference between the two groups is negligible. The very small differences, which persist despite adjustment for age, may be statistically significant partly because of the large sample size. Statistically significant differences were also found for the Map search 1st minute right, with medians of 0.00 and 2.00. On closer examination of the data, the unusual medians could be explained: it appeared that those who scored highly on Map search 1st minute left scored poorly on Map search 1st minute right and vice versa,

which is logical considering that when most participants begin circling objects on one side of the map, they continue to circle on that side of the map for almost one minute. However, this does not explain why those with and without CHD scored differently. Finally, there were statistically significant differences between medians for the telephone task time taken sub-test, which is discussed later. Overall, for the majority of subtests, there was no strong evidence suggesting an association between CHD and neuropsychological test score results in the whole population.

Table 7.8: Medians (and significance of difference between medians) for those with and without proxies for coronary heart disease (CHD) for each of the cognitive function tests

Neuropsychological Test	**Medians for 'Any record of CHD?'**			**Medians for 'If CHD any Hx MI?'** (diagnosis of CHD in GP notes and had suffered one or more myocardial infarctions)			**Medians for ' If CHD any Hx angina?'** (diagnosis of CHD and a diagnosis of angina in GP notes)		
	Yes	**No**	**p-value**	**Yes**	**No**	**p-value**	**Yes**	**No**	**p-value**
MMSE	29.00	29.00	0.02*	29.00	29.00	0.74	29.00	29.00	0.014*
Logical Memory Immediate (raw)	15.00	14.00	0.76	15.50	14.00	0.15	15.00	14.00	0.40
Logical Memory Immediate (%)	21.00	16.50	0.63	21.00	17.00	0.14	21.00	16.00	0.33
Logical Memory Delayed (raw)	11.00	10.00	0.78	11.00	10.00	0.45	11.00	10.00	0.51
Logical Memory Delayed (%)	36.00	36.00	0.77	37.50	36.00	0.46	36.00	36.00	0.60
Rey Complex Figure Copy	34.00	34.00	0.74	34.00	33.00	0.54	33.00	34.00	0.50
Rey Complex Figure Delayed	12.00	12.75	0.67	12.50	12.50	0.58	12.00	13.00	0.53
Map Search (1st Minute, Left)	17.00	18.00	0.33	17.00	17.00	0.41	17.00	17.00	0.45
Map Search (1st Minute, Right)	0.00	2.00	0.008*	0.00	1.00	0.15	0.00	1.50	0.03*
Map Search (2nd Minute, Left	9.00	8.00	0.97	9.00	9.00	0.48	9.00	8.50	0.90
Map Search (2nd Minute, Right)	7.00	8.00	0.84	5.00	8.00	0.51	7.00	8.00	0.70
Telephone Task No. of Targets	18.00	18.00	0.26	18.00	18.00	0.80	18.00	18.00	0.31
Telephone Task Time Taken (seconds)	91.00	88.00	0.036*	92.50	88.00	0.49	94.00	88.00	0.008*
Telephone Task Dual Task Decrement	2.10	2.15	0.73	1.800	2.200	0.48	2.10	2.15	0.64
NART No. of Errors	21.00	20.50	0.71	20.00	21.00	0.24	21.00	20.50	0.54
NART Predicted IQ	105.00	105.00	0.83	106.00	105.00	0.18	105.00	105.00	0.61
Digit Span	14.00	13.00	0.24	13.00	13.00	0.30	13.00	13.00	0.57
PASAT (2.4-seconds)	28.00	29.50	0.59	28.00	29.00	0.78	28.00	30.00	0.30
PASAT (1.2-seconds)	11.00	7.50	0.25	12.00	8.00	0.55	10.00	8.00	0.60

* Significant difference between groups ($p \leq 0.05$)

b) Effect of diabetes on the neuropsychological test results of the whole population

(Table 7.9)

There were no significant differences between those with and without a record of diabetes for any of the neuropsychological tests.

Table 7.9: Medians (and significance of difference between medians) for those with and without GP record of diabetes for each of the cognitive function tests

Neuropsychological Test	Median values for 'Any record of diabetes?' (2dp)		
	Yes	No	p-value
MMSE	29.00	29.00	0.31
Logical Memory Immediate (raw)	14.00	15.00	0.80
Logical Memory Immediate (%)	16.50	17.00	0.87
Logical Memory Delayed (raw)	11.00	10.00	0.80
Logical Memory Delayed (%)	28.00	36.00	0.50
Rey Complex Figure Copy	33.50	33.00	0.90
Rey Complex Figure Delayed	13.75	12.50	0.60
Map Search (1st Minute, Left)	16.50	17.00	0.83
Map Search (1st Minute, Right)	0.00	1.00	0.34
Map Search (2nd Minute, Left	10.00	8.00	0.09
Map Search (2nd Minute, Right)	6.50	8.00	0.70
Telephone Task No. of Targets	18.00	18.00	0.91
Telephone Task Time Taken (seconds)	97.50	88.00	0.10
Telephone Task Dual Task Decrement	2.30	2.10	0.98
NART No. of Errors	19.50	21.00	1.00
NART Predicted IQ	106.50	105.00	0.99
Digit Span	13.00	13.00	0.29
PASAT (2.4-seconds)	30.00	29.00	0.80
PASAT (1.2-seconds)	12.00	8.00	0.78

c) Effect of hypertension on the neuropsychological test results of the whole population (Table 7.10)

One proxy for hypertension was whether or not there was GP documentation of current prescription of medication specifically for hypertension. There were no significant differences between those who did and did not take medication to treat hypertension for any of the neuropsychological tests.

Table 7.10: Medians (and significance of difference between medians) for those who were and were not taking medication for hypertension for each of the cognitive function tests

Neuropsychological Test	Median values for 'medication for hypertension?' (2dp)		
	Yes	No	p-value
MMSE	29.00	29.00	0.21
Logical Memory Immediate (raw)	14.00	15.00	0.88
Logical Memory Immediate (%)	17.00	17.00	0.64
Logical Memory Delayed (raw)	10.00	10.00	0.98
Logical Memory Delayed (%)	36.00	36.00	0.64
Rey Complex Figure Copy	33.00	34.00	0.24
Rey Complex Figure Delayed	12.00	12.50	0.57
Map Search (1st Minute, Left)	17.00	17.00	0.78
Map Search (1st Minute, Right)	0.00	1.00	0.09
Map Search (2nd Minute, Left	9.00	9.00	0.79
Map Search (2nd Minute, Right)	8.00	6.00	0.60
Telephone Task No. of Targets	18.00	18.00	0.45
Telephone Task Time Taken (seconds)	90.50	88.00	0.25
Telephone Task Dual Task Decrement	1.90	2.20	0.71
NART No. of Errors	20.00	21.00	0.19
NART Predicted IQ	106.00	105.00	0.14
Digit Span	14.00	13.00	0.39
PASAT (2.4-seconds)	29.00	29.00	0.51
PASAT (1.2-seconds)	7.00	8.50	0.80

d) Effect of heart failure on the neuropsychological test results of the whole population.

(Table 7.11)

There was a statistically significant difference (p=0.047) in the scores for the Digit span test between those who did (median = 11.50) and did not (median = 13.00) have a record of symptomatic heart failure in the last three months in their GP notes. There were no other significant differences between the groups. Since Digit span measures attention and no other tests of attention demonstrated significant differences, and since this was the only test to show any significant differences between people with and without CHF, it is reasonable not to attach great importance to this finding. Overall, there does not appear to be an association between heart failure and cognitive function for the total population.

Table 7.11: Medians (and significance of difference between medians) for those who did and did not have proxies for heart failure for each of the cognitive function tests

Neuropsychological Test	Median values for 'any symptomatic heart failure in the last three months?' (2dp)		
	Yes	No	p-value
MMSE	29.00	29.00	0.70
Logical Memory Immediate (raw)	16.00	14.00	0.22
Logical Memory Immediate (%)	23.50	17.00	0.17
Logical Memory Delayed (raw)	11.50	10.00	0.27
Logical Memory Delayed (%)	37.00	36.00	0.33
Rey Complex Figure Copy	33.00	34.00	0.65
Rey Complex Figure Delayed	12.00	12.50	0.90
Map Search (1st Minute, Left)	17.50	17.00	0.88
Map Search (1st Minute, Right)	0.00	0.00	0.75
Map Search (2nd Minute, Left	11.50	9.00	0.14
Map Search (2nd Minute, Right)	8.50	7.00	0.92
Telephone Task No. of Targets	19.00	18.00	0.53
Telephone Task Time Taken (seconds)	94.00	88.00	0.58
Telephone Task Dual Task Decrement	2.350	2.100	0.76
NART No. of Errors	15.50	21.00	0.10
NART Predicted IQ	111.50	105.00	0.09
Digit Span	11.50	13.00	0.05*
PASAT (2.4-seconds)	28.00	29.00	0.69
PASAT (1.2-seconds)	9.00	8.00	0.64

* Significant difference between groups ($p \leq 0.05$)

e) Effect of duration of atrial fibrillation on the neuropsychological test results of all cases (Table 7.12)

Pearson's and Spearman's Correlations were used to assess the effect of duration of atrial fibrillation (taken from GP notes) on the individual cognitive function tests. The results were not significant for all neuropsychological tests except for telephone task time taken. For this test, the score correlated significantly (0.048) with duration of AF, however the correlation coefficient was very small (R=0.151). Therefore there was no overall association between duration of AF and cognitive decline for the total population (cases only).

Table 7.12: Pearson's and Spearman's Correlation for the effect of duration of atrial fibrillation on test scores (2dp)

Neuropsychological Test	Pearson's Correlation	Spearman's Correlation	p-value for Spearman's Correlation
MMSE	-	-0.04	0.64
Logical Memory Immediate (raw)	0.09	0.09	0.23
Logical Memory Immediate (%)	-	0.10	0.20
Logical Memory Delayed (raw)	0.07	0.07	0.34
Logical Memory Delayed (%)	-	0.11	0.16
Rey Complex Figure Copy	0.06	0.07	0.36
Rey Complex Figure Delayed	0.06	0.04	0.65
Map Search (1st Minute, Left)	-0.04	-0.06	0.49
Map Search (1st Minute, Right)	-0.04	-0.03	0.75
Map Search (2nd Minute, Left)	0.008	0.004	0.96
Map Search (2nd Minute, Right)	-0.11	-0.10	0.21
Telephone Task No. of Targets	0.03	0.03	0.73
Telephone Task Time Taken	0.06	0.15	0.05*
Telephone Task Dual Task Decrement	0.00	0.01	0.98
NART No. of Errors	-0.01	-0.03	0.67
NART Predicted IQ	0.01	0.03	0.66
Digit Span	-0.05	-0.004	0.96
PASAT (2.4-seconds)	0.00	0.03	0.68
PASAT (1.2-seconds)	0.01	0.02	0.82

* Significant difference between groups ($p \leq 0.05$)

f) Effect of cholesterol on the neuropsychological test results of the whole population (Table 7.13)

Pearson's and Spearman's Correlations were used to assess the effect of non-fasting cholesterol (sample taken at baseline visit) on the individual cognitive function tests. For the majority of neuropsychological tests there was no correlation between score and cholesterol. Using Pearson's technique, cholesterol did correlate significantly with map search 2nd minute right (p= 0.040) and telephone task time taken (p=0.027). However when Spearman's technique, which is more appropriate for non-normal data, was used there were no significant results. Therefore there was no strong evidence to support an association between cholesterol level and cognitive function in the total population.

Table 7.13: Pearson's and Spearman's Correlation for the effect of cholesterol on test scores (2dp).

Neuropsychological Test	Pearson's Correlation	p-value for Pearson's Correlation	Spearman's Correlation	p-value for Spearman's Correlation
MMSE	0.04	0.46	0.03	0.67
Logical Memory Immediate (raw)	-0.07	0.21	-0.03	0.66
Logical Memory Immediate (%)	-0.06	0.29	-0.02	0.75
Logical Memory Delayed (raw)	-0.02	0.73	0.03	0.66
Logical Memory Delayed (%)	-0.02	0.79	0.01	0.82
Rey Complex Figure Copy	0.03	0.66	0.01	0.87
Rey Complex Figure Delayed	-0.06	0.27	-0.07	0.26
Map Search (1st Minute, Left)	0.08	0.20	0.08	0.17
Map Search (1st Minute, Right)	0.07	0.26	0.04	0.48
Map Search (2nd Minute, Left)	-0.07	0.26	-0.07	0.22
Map Search (2nd Minute, Right)	0.12	0.04*	0.12	0.07
Telephone Task No. of Targets	0.02	0.75	-0.003	0.96
Telephone Task Time Taken	-0.13	0.03*	-0.11	0.06
Telephone Task Dual Task Decrement	-0.07	0.23	-0.04	0.54
NART No. of Errors	-0.05	0.38	-0.03	0.59
NART Predicted IQ	0.02	0.78	0.01	0.81
Digit Span	-0.01	0.82	-0.03	0.60
PASAT (2.4-seconds)	0.24	0.24	-0.06	0.28
PASAT (1.2-seconds)	-0.03	0.64	-0.04	0.52

* Significant difference between groups ($p \leq 0.05$)

g) Effect of health status (SF-36 score) on the neuropsychological test results of the whole population

The Short Form -36 (SF-36) was used to measure health status. Raw scores were transformed into the seven 'domains' of health status (physical functioning, role physical, bodily pain, general health, vitality, role emotional, mental health) using algorithms.[298] The effect of health status on cognitive function at baseline was analysed using Spearman's correlation techniques. There was very little relationship between transformed SF-36 scores and neuropsychological test scores for the whole population. The greatest correlation was for the effect of SF-36 emotion domain on the sub-test 'telephone task time taken'; however even for this sub-test the correlations were very weak, with the largest coefficient being –0.188 ($p<0.01$).

Therefore overall, there was no evidence to suggest that SF-36 transformed score confounds measurement of cognitive function in the total population.

h) Effect of education on the neuropsychological test results of the whole population (Table 7.14)

i) Effect of the variable "How old were you when you left continuous full-time education"

The effect of education on cognition was addressed by analysing the effect of the baseline variables, "How old were you when you left continuous full-time education?" and "Highest qualification".

Using Spearman's Correlation techniques, an association between leaving school at an older age and better cognitive function test scores was demonstrated (see table 7.14). This association was small because the majority of people left school at 14 years or under, skewing the distribution of the scores. The correlation coefficients, though highly significant for these cognitive function tests, are small in size, suggesting the association is weak.

Table 7.14: Spearman's Correlation for the effect of education on test scores (2dp)

Neuropsychological Test	Spearman's Correlation	p-value for Spearman's Correlation
MMSE	0.24	0.00*
Logical Memory Immediate (raw)	0.17	0.00*
Logical Memory Immediate (%)	0.13	0.01*
Logical Memory Delayed (raw)	0.17	0.001*
Logical Memory Delayed (%)	0.12	0.03*
Rey Complex Figure Copy	0.18	0.001*
Rey Complex Figure Delayed	0.20	0.00*
Map Search (1st Minute, Left)	0.19	0.001*
Map Search (1st Minute, Right)	0.05	0.54
Map Search (2nd Minute, Left)	0.02	0.72
Map Search (2nd Minute, Right)	0.13	0.03*
Telephone Task No. of Targets	0.07	0.16
Telephone Task Time Taken	-0.19	0.00*
Telephone Task Dual Task Decrement	-0.07	0.18
NART No. of Errors	-0.31	0.00*
NART Predicted IQ	0.30	0.00*
Digit Span	0.18	0.001*
PASAT (2.4-seconds)	0.23	0.00*
PASAT (1.2-seconds)	0.06	0.23

* Significant difference between groups ($p \leq 0.05$)

ii) Effect of the variable "What is your highest qualification?"

The majority (70.2%) of participants had no qualifications (described in Chapter 6). The remaining categories of qualifications (school qualifications, degree, apprenticeship etc, described elsewhere) therefore contained small numbers, making it difficult to examine the effect of each of the individual qualification categories on cognitive function tests. Therefore the categories were analysed as two groups: 'no qualifications' and 'any qualifications'. The analysis was performed twice, firstly considering apprenticeship in the 'any qualifications' group (table 7.15), secondly considering apprenticeship in the 'no qualifications' group (table 7.16). Mann-Whitney tests were performed to determine whether the difference in means between those with and without 'any qualifications' was statistically significant (table 7.15). Those with any qualifications (regardless of

whether apprenticeship was included as 'some qualifications' or 'no qualifications') performed significantly better on nearly all cognitive function tests than those with no qualifications (see tables 7.15 and 7.16).

Table 7.15: Means (and significance of difference between means) for those with and without qualifications for each of the cognitive function tests), with apprenticeship counted as a qualification.

Neuropsychological Test	Mean scores		
	No qualifications	Some qualifications (including apprenticeship)	P-value (using Mann-Whitney – based on medians not shown here)
MMSE	28.27	28.82	0.001*
Logical Memory Immediate (raw)	14.10	15.91	0.01*
Logical Memory Immediate (%)	23.50	29.51	0.01*
Logical Memory Delayed (raw)	10.29	12.20	0.01*
Logical Memory Delayed (%)	34.39	41.26	0.01*
Rey Complex Figure Copy	31.16	33.64	0.00*
Rey Complex Figure Delayed	11.88	15.86	0.00*
Map Search (1st Minute, Left)	15.51	19.50	0.00*
Map Search (1st Minute, Right)	5.12	5.60	0.31
Map Search (2nd Minute, Left)	9.44	9.56	0.70
Map Search (2nd Minute, Right)	8.33	11.37	0.006*
Telephone Task No. of Targets	17.37	17.93	0.02*
Telephone Task Time Taken (seconds)	104.57	83.85	0.00*
Telephone Task Dual Task Decrement	4.86	2.456	0.054
NART No. of Errors	23.15	18.39	0.00*
NART Predicted IQ	101.89	107.13	0.00*
Digit Span	13.29	14.56	0.003*
PASAT (2.4-seconds)	26.58	37.25	0.00*
PASAT (1.2-seconds)	11.61	14.27	0.11

* Significant difference between groups ($p \leq 0.05$)

Table 7.16: Means (and significance of difference between means) for those with and without qualifications for each of the cognitive function tests), with apprenticeship *not* counted as a qualification.

Neuropsychological Test	Mean scores		
	No qualifications (including apprenticeship)	Some qualifications	P-value (using Mann-Whitney– based on medians not shown here)
MMSE	28.27	28.96	0.00*
Logical Memory Immediate (raw)	14.45	16.26	0.004*
Logical Memory Immediate (%)	23.54	31.02	0.003*
Logical Memory Delayed (raw)	10.34	12.56	0.003*
Logical Memory Delayed (%)	34.68	42.19	0.01*
Rey Complex Figure Copy	31.40	33.58	0.00*
Rey Complex Figure Delayed	12.30	15.58	0.00*
Map Search (1st Minute, Left)	15.94	19.19	0.01*
Map Search (1st Minute, Right)	5.07	5.88	0.21
Map Search (2nd Minute, Left)	9.41	9.70	0.72
Map Search (2nd Minute, Right)	8.58	11.38	0.02*
Telephone Task No. of Targets	17.45	17.81	0.18
Telephone Task Time Taken (seconds)	102.91	83.60	0.00*
Telephone Task Dual Task Decrement	4.71	2.282	0.04
NART No. of Errors	23.48	16.07	0.00*
NART Predicted IQ	101.49	109.81	0.00*
Digit Span	13.23	15.11	0.003*
PASAT (2.4-seconds)	27.23	38.06	0.00*
PASAT (1.2-seconds)	11.45	15.50	0.04*

* Significant difference between groups ($p \leq 0.05$)

Overall, those with highest educational level performed significantly better than those with less education.

However, the CAFÉ participants have a highly skewed distribution for these variables, with the majority of participants having no qualifications and having left school at age 14 years or under. Therefore it is likely that education, although it may significantly affect cognition, will not greatly confound the results for CAFÉ because most participants have the same level of education, with similar distributions for both cases and controls.

Summary of total population confounder analyses

Upon analysing the effect of CHD, diabetes, hypertension, heart failure, duration of AF, cholesterol, and health status we found no strong evidence to suggest that these variables would confound the measurement of cognitive function in the total study population.

For education, there was an association between highest qualification / age at leaving education and cognitive function. However, because this sample consists predominantly of those within the same educational category, it is unlikely that this variable will confound our results. Nonetheless, this analysis has identified a potential source of confounding and adjustment for education was made in subsequent analyses of cognitive function.

2. Assessment of key confounders as covariates to investigate their effect on the relationship between case status and cognitive function

The next stage was to determine whether or not the key confounders had an effect on the (age-adjusted) relationships already described between cases and controls and cognitive function.

Because the data was predominantly non-normal, this was done using non-parametric tests. For categorical variables, Mann-Whitney tests were performed to determine whether or not there were significant differences between those with and without the confounding variable for both cases and controls, with the confounding variable incorporated into the model as a covariate. Where a significant difference was found, the frequencies of the confounding variables for cases and controls were examined to determine the actual difference between the two groups. For continuous variables, Spearman's and Pearson's correlations were used.

a) Coronary Heart Disease

The results of Mann-Whitney tests are shown in Table 7.17a. There were no significant differences between those with and without proxies for CHD for both cases and controls for most neuropsychological tests.

The exceptions to this were the MMSE and telephone task time taken. For the MMSE (tables 7.17a, 7.17b), cases without a record of CHD performed significantly better ($p=0.021$) than cases with CHD (28.69 versus 28.12); and cases without a history of angina performed significantly ($p=0.027$) better than cases with angina (28.68 versus 28.06). For the 'telephone task time taken' subtest (table 7.17c), cases without any history of angina performed significantly ($p=0.029$) better than cases with angina (98.57 seconds versus 114.26 seconds). There was no difference for controls.

Overall, there were no significant differences between those with and without proxies for CHD that were consistent across all three proxies, and for those findings which were statistically significant

the actual differences between the means were very small and therefore clinically insignificant (except angina history for the telephone task time taken sub-test). Therefore there is no strong evidence that proxies for CHD affect the relationship between case status and cognitive function.

Table 7.17a : Significance levels (using Mann-Whitney) for the difference in cognitive function scores for those (cases and controls) with and without proxies for CHD.

Neuropsychological test	P-values for difference between those with and without proxies for CHD (using Mann- Whitney) (2dp)					
	'Any record of CHD?'		'If CHD any Hx MI?'		'If CHD any Hx angina?'	
	Control	Case	Control	Case	Control	Case
MMSE	0.32	0.02*	0.44	0.75	0.20	0.03*
Logical Memory Immediate (raw)	0.57	0.98	0.23	0.43	0.32	0.74
Logical Memory Immediate (%)	0.42	0.96	0.15	0.51	0.23	0.75
Logical Memory Delayed (raw)	0.92	0.59	0.76	0.43	0.91	0.40
Logical Memory Delayed (%)	0.96	0.70	0.66	0.53	0.87	0.55
Rey Complex Figure Copy	0.98	0.76	0.82	0.51	0.79	0.56
Rey Complex Figure Delayed	0.42	0.73	0.63	0.78	0.70	0.69
Map Search (1st Minute, Left)	0.61	0.56	0.27	0.99	0.99	0.37
Map Search (1st Minute, Right)	0.12	0.03	0.50	0.18	0.07	0.28
Map Search (2nd Minute, Left)	0.80	0.85	0.28	0.96	0.86	0.79
Map Search (2nd Minute, Right)	0.42	0.54	0.19	0.71	0.40	0.71
Telephone Task No. of Targets	0.43	0.42	0.68	0.45	0.68	0.31
Telephone Task Time Taken (seconds)	0.38	0.12	0.85	0.54	0.22	0.03*
Telephone Task Dual Task Decrement	0.39	0.24	0.36	0.93	0.33	0.14
NART No. of Errors	0.89	0.60	0.08	1.00	0.79	0.33
NART Predicted IQ	0.74	0.60	0.06	0.93	0.65	0.29
Digit Span	0.23	0.58	0.16	0.98	0.31	0.88
PASAT (2.4-seconds)	0.83	0.57	0.86	0.58	0.53	0.34
PASAT (1.2-seconds)	0.40	0.44	0.32	0.80	0.70	0.73

* Significant difference between groups ($p \leq 0.05$)

Table 7.17b: Mean scores for significant results on Mann-Whitney tests (MMSE)

Neuropsychological test	Mean score for cases	
	'Any record of CHD?' - Yes	'Any record of CHD?' - No
MMSE	28.12	28.69

Table 7.17c: Mean scores for significant results on Mann-Whitney tests (telephone task time taken)

Neuropsychological test	Mean score for cases	
	'If CHD any Hx angina?' Yes	'If CHD any Hx angina?' No
MMSE	28.06	28.68
Telephone task time taken	114.26	98.57

b) Diabetes

The results of Mann-Whitney tests are shown in Table 7.18a. There were no significant differences between those with and without diabetes for both cases and controls for most neuropsychological tests. The only exception to this was the 'Map Search 2nd minute, left', where controls with diabetes scored significantly (p=0.028) better than controls without diabetes (14.11 versus 9.75) (table 7.18b). However there were no significant findings for the other map search sub-tests, which we would have expected if this finding were of importance.

Therefore, overall there was no evidence to suggest that diabetes affects the relationship between case status and cognitive function.

Table 7.18a : Significance levels (using Mann-Whitney) for the difference in cognitive function scores for those (cases and controls) with and without diabetes.

	P-values for difference between those with and without diabetes (using Mann- Whitney)	
	Control	**Case**
MMSE	0.33	0.52
Logical Memory Immediate (raw)	0.66	0.80
Logical Memory Immediate (%)	0.75	0.82
Logical Memory Delayed (raw)	0.88	0.66
Logical Memory Delayed (%)	0.23	0.998
Rey Complex Figure Copy	0.79	0.91
Rey Complex Figure Delayed	0.47	0.71
Map Search (1st Minute, Left)	0.68	0.82
Map Search (1st Minute, Right)	0.44	0.54
Map Search (2nd Minute, Left)	0.03*	0.41
Map Search (2nd Minute, Right)	0.33	0.77
Telephone Task No. of Targets	0.11	0.29
Telephone Task Time Taken (seconds)	0.47	0.38
Telephone Task Dual Task Decrement	0.50	0.77
NART No. of Errors	0.99	0.90
NART Predicted IQ	0.95	0.94
Digit Span	0.28	0.62
PASAT (2.4-seconds)	0.68	0.55
PASAT (1.2-seconds)	0.33	0.31

* Significant difference between groups ($p \leq 0.05$)

Table 7.18b: Mean scores for significant results on Mann-Whitney tests (Map Search 2nd minute, Left)

Neuropsychological test	Mean score for controls	
	'Any record of diabetes?' - Yes	**'Any record of diabetes?' - No**
Map Search 2nd minute, Left	14.11	9.75

c) Hypertension

There were no significant differences between those with and without hypertension (using current prescription for hypertension as a proxy for hypertension) for both cases and controls for all neuropsychological tests (table 7.19). Therefore, there was no evidence to suggest that hypertension affects the relationship between case status and cognitive function.

Table 7.19: Significance levels (using Mann-Whitney) for the difference in cognitive function scores for those (cases and controls) with and without hypertension.

	P-values for difference between those with and without hypertension (using Mann- Whitney) (2dp)	
	Control	**Case**
MMSE	0.52	0.26
Logical Memory Immediate (raw)	0.995	0.66
Logical Memory Immediate (%)	0.91	0.53
Logical Memory Delayed (raw)	0.98	0.98
Logical Memory Delayed (%)	0.88	0.62
Rey Complex Figure Copy	0.12	0.94
Rey Complex Figure Delayed	0.57	0.89
Map Search (1st Minute, Left)	0.94	0.89
Map Search (1st Minute, Right)	0.33	0.17
Map Search (2nd Minute, Left)	0.75	0.92
Map Search (2nd Minute, Right)	0.27	0.79
Telephone Task No. of Targets	0.12	0.60
Telephone Task Time Taken (seconds)	0.32	0.73
Telephone Task Dual Task Decrement	0.08	0.27
NART No. of Errors	0.29	0.39
NART Predicted IQ	0.23	0.36
Digit Span	0.27	0.88
PASAT (2.4-seconds)	0.89	0.49
PASAT (1.2-seconds)	0.51	0.71

* Significant difference between groups ($p \leq 0.05$)

d) Heart Failure

The results of Mann-Whitney tests are shown in Table 7.20a. There were no significant differences between those with and without heart failure for both cases and controls for most neuropsychological tests.

The only exceptions to this were the 'Map Search 2nd minute, left' (cases) , PASAT-2.4 seconds (controls) and PASAT-1.2 seconds (controls). For 'Map Search 2nd minute, left', cases with heart failure scored significantly (p=0.039) better than cases without heart failure (12.10 versus 8.62) (table 7.20b). However there were no significant findings for the other map search sub-tests, which we would have expected if this finding were of importance. For PASAT-2.4 seconds and PASAT-1.2 seconds, the numbers were very small - only 3 controls with heart failure versus 138 controls

without, therefore we decided that it was unlikely that heart failure would have an important effect on our findings.

Therefore, overall there was no evidence to suggest that heart failure affects the relationship between case status and cognitive function.

Table 7.20a: Significance levels (using Mann-Whitney) for the difference in cognitive function scores for those (cases and controls) with and without proxies for heart failure.

	P-values for difference between those with and without heart failure (using Mann- Whitney) (2dp)	
	Control	**Case**
MMSE	0.44	0.86
Logical Memory Immediate (raw)	0.67	0.09
Logical Memory Immediate (%)	0.77	0.07
Logical Memory Delayed (raw)	0.97	0.20
Logical Memory Delayed (%)	0.37	0.14
Rey Complex Figure Copy	0.05	0.60
Rey Complex Figure Delayed	0.78	0.80
Map Search (1st Minute, Left)	0.29	0.97
Map Search (1st Minute, Right)	0.32	0.91
Map Search (2nd Minute, Left)	0.67	0.04*
Map Search (2nd Minute, Right)	0.58	0.95
Telephone Task No. of Targets	0.08	0.96
Telephone Task Time Taken (seconds)	0.06	0.36
Telephone Task Dual Task Decrement	0.16	0.32
NART No. of Errors	0.18	0.16
NART Predicted IQ	0.18	0.18
Digit Span	0.13	0.15
PASAT (2.4-seconds)	0.01*	0.45
PASAT (1.2-seconds)	0.05*	0.16

* Significant difference between groups ($p \leq 0.05$)

Table 7.20b: Mean scores for significant results on Mann-Whitney tests (Map Search 2nd minute, Left)

Neuropsychological test	Mean score for controls	
	Heart failure? - Yes	**Heart failure? - No**
Map Search 2nd minute, Left	12.10	8.62

f) Cholesterol (Table 7.21)

For nearly all neuropsychological tests and for both cases and controls, there were no significant correlations between cholesterol level and test score. The only exceptions to this were for Rey Complex Figure Delayed (controls) and telephone task time taken (cases) where the correlation was statistically significant (0.012 and 0.032 respectively). However, for both of these tests, the correlation coefficient itself was very small (-0.198 and -0.184) therefore these findings are not clinically important. Overall, there is no evidence to suggest that cholesterol confounds the relationship between case status and cognitive function.

Table 7.21: Spearman's Correlation for the effect of cholesterol on test scores for cases and controls.

Neuropsychological Test	Cases (2dp)		Controls (2dp)	
	Spearman's Correlation	p-value for Spearman's Correlation	Spearman's Correlation	p-value for Spearman's Correlation
MMSE	0.07	0.42	-0.02	0.77
Logical Memory Immediate (raw)	0.05	0.53	-0.11	0.16
Logical Memory Immediate (%)	0.06	0.52	-0.10	0.21
Logical Memory Delayed (raw)	0.08	0.34	-0.03	0.76
Logical Memory Delayed (%)	0.08	0.38	-0.05	0.54
Rey Complex Figure Copy	0.04	0.63	-0.04	0.59
Rey Complex Figure Delayed	0.06	0.50	-0.20	0.01*
Map Search (1st Minute, Left)	0.11	0.18	0.012	0.88
Map Search (1st Minute, Right)	0.05	0.56	0.01	0.95
Map Search (2nd Minute, Left)	-0.10	0.24	-0.05	0.52
Map Search (2nd Minute, Right)	0.15	0.07	0.04	0.61
Telephone Task No. of Targets	0.08	0.35	-0.09	0.26
Telephone Task Time Taken	-0.18	0.03*	0.04	0.61
Telephone Task Dual Task Decrement	-0.09	0.29	0.01	0.86
NART No. of Errors	-0.10	0.26	0.05	0.50
NART Predicted IQ	0.10	0.23	-0.09	0.28
Digit Span	0.02	0.81	-0.07	0.41
PASAT (2.4-seconds)	0.02	0.85	-0.12	0.12
PASAT (1.2-seconds)	-0.01	0.92	-0.06	0.45

* Significant difference between groups ($p \leq 0.05$)

g) Health status (Table 7.22)

As described previously, SF-36 raw scores were transformed into the seven 'domains' of health status (physical activity, role-physical, bodily pain, general health, vitality, emotion, mental health). Mann-Whitney tests demonstrated that cases and controls had significantly different scores in that cases had poorer scores than controls on all analysed components of the SF-36 form (limited physical activities due to health ($p<0.001$), problems in the last 4 weeks due to physical ($p<0.001$) and emotional ($p<0.001$) health, perspective on general health ($p<0.01$) and in comparison to others ($p<0.001$)); except for pain, where a poorer score in cases was non-significant ($p=0.1$).

Table 7.22: Mean transformed SF-36 scores for cases and controls for each of the seven SF-36 domains (2dp)

SF-36 domain	Mean transformed SF-36 score (SD)		P-values for difference between cases and controls (using Mann-Whitney)
	Controls	Cases	
Physical Functioning	66.21 (28.96)	50.86 (30.00)	0.00*
Role Physical	71.51 (37.77)	56.54 (40.25)	0.00*
Bodily Pain	65.86 (25.58)	58.63 (28.75)	0.12
General health	62.66 (18.54)	56.58 (21.33)	0.01*
Vitality	67.83 (19.74)	59.08 (26.81)	0.00*
Role Emotional	89.31 (28.74)	77.90 (36.89)	0.00*
Mental health	71.57 (12.11)	66.68 (14.51)	0.00*

Significant difference between groups ($p \leq 0.05$)

Spearman's correlations were then performed to determine whether these differences had an impact on the relationship between case status and cognitive function test score.

There was very little relationship between transformed SF-36 scores and neuropsychological test scores for both cases and controls. The greatest correlation was for SF-36 and sub-test 'telephone task time taken'; however even for this sub-test the correlations were very weak, with the largest coefficient being –0.281 ($p=0.00$).

Therefore overall, there was no evidence to suggest that SF-36 transformed score counfounds the relationship between case status and cognitive function.

h) Education

Spearman's correlations for education (age at leaving continuous full-time education) are shown in table 7.23. Although there a number of statistically significant correlations, the correlation coefficients are small, with the largest being -0.329. In addition, similar proportions of cases (62.3%) and controls (68.3%) completed their education at 14 years or under. This suggests that education is unlikely to significantly affect the relationship between case status and cognitive function. Nonetheless, this analysis has identified a potential source of confounding and therefore adjustment for education was made in subsequent analyses of cognitive function for cases and controls.

Table 7.23: Spearman's Correlation for the effect of education on test scores for cases and controls. (2dp)

Neuropsychological Test	Cases		Controls	
	Spearman's Correlation	p-value for Spearman's Correlation	Spearman's Correlation	p-value for Spearman's Correlation
MMSE	0.21	0.005*	0.26	0.00*
Logical Memory Immediate (raw)	0.19	0.01*	0.13	0.07
Logical Memory Immediate (%)	0.16	0.04*	0.10	0.18
Logical Memory Delayed (raw)	0.16	0.03*	0.20	0.008*
Logical Memory Delayed (%)	0.11	0.17*	0.13	0.09
Rey Complex Figure Copy	0.23	0.002*	0.14	0.07
Rey Complex Figure Delayed	0.16	0.03*	0.23	0.002*
Map Search (1st Minute, Left)	0.06	0.41	0.26	0.00*
Map Search (1st Minute, Right)	0.09	0.23	0.05	0.52
Map Search (2nd Minute, Left)	0.05	0.53	0.05	0.50
Map Search (2nd Minute, Right)	0.10	0.17	0.07	0.32
Telephone Task No. of Targets	0.05	0.49	0.09	0.24
Telephone Task Time Taken	-0.15	0.05	-0.23	0.002*
Telephone Task Dual Task Decrement	-0.10	0.19	-0.09	0.23
NART No. of Errors	-0.30	0.00*	-0.33	0.00*
NART Predicted IQ	0.30	0.00*	0.31	0.00*
Digit Span	0.25	0.001*	0.12	0.11
PASAT (2.4-seconds)	0.19	0.01*	0.28	0.00*
PASAT (1.2-seconds)	0.09	027	0.05	0.54*

* Significant difference between groups ($p \leq 0.05$)

Summary of case / control confounder analysis

Key confounders (CHD, diabetes, hypertension, heart failure, cholesterol and health status) had little effect on cognitive function for both cases and controls. Therefore there is no evidence that these variables will affect the conclusions derived from the age-adjusted comparisons between cases and controls. The one exception to this was education, which demonstrated a significant, though small effect on cognitive function for both cases and controls on some sub-tests. Therefore adjustment for education was made on subsequent analyses of neuropsychological test results for cases and controls.

3. Assessment of key confounders as covariates to investigate their effect on the relationship between treatment subgroups (aspirin/ warfarin/ neither) and cognitive function.

Finally, it was necessary to determine whether or not the key confounders had an effect on the (age-adjusted) relationships already described between cognitive function and the five subgroups on aspirin, warfarin or neither treatment (case warfarin (n=89), case aspirin (n=61), case neither (n=25), control aspirin (n=56), control neither (n=131)). As for the case/control analyses, this was done using non-parametric tests. For categorical variables, Mann-Whitney tests were performed to determine whether or not there were significant differences between subgroups when the confounding variable was incorporated into the model as a covariate. Where a significant difference was found, the frequencies of the confounding variables for subgroups were examined to determine the actual difference between the five groups. For continuous variables, Spearman's and Pearson's correlations were used. Most of the tables for the subgroup confounding analyses are not shown here since five subgroups generated vast tables which would be difficult to follow in a thesis such as this.

a) Coronary Heart Disease

Mann-Whitney tests demonstrated few significant differences between those with and without proxies for CHD in all five subgroups for most neuropsychological tests. The only statistically significant differences were that: controls (not on aspirin or warfarin) without CHD performed significantly (p=0.043) better than controls (not on aspirin or warfarin) with CHD (mean 9.84 versus 5.53) on map search 2nd minute right; controls (not on aspirin or warfarin) without CHD performed significantly (p=0.015) better than controls (not on aspirin or warfarin) with CHD on telephone task time taken (mean 91.61 versus 110.07 seconds); aspirin cases without CHD

performed significantly (p=0.033) better than aspirin cases with CHD on NART errors (mean 20.00 versus 25.36); and aspirin cases with CHD performed significantly (p=0.039) better than aspirin cases without CHD on NART IQ (mean 106.09 versus 99.36). When 'if CHD, any record of angina?' rather than 'any record of CHD?' was used as a proxy variable, an identical pattern emerged with the same subgroups showing significant differences on the same (few) tests. When the variable 'if CHD, any record of MI?' was used, a different pattern emerged, with the only significant differences being that: controls (not on aspirin or warfarin) with MIs performed significantly (p=0.048) better than controls (not on aspirin or warfarin) without MIs (mean 41.90 versus 25.44) on the Logical Memory immediate (%); aspirin controls with MIs performed significantly (p=0.041) better than aspirin controls without MIs (mean 79.60 versus 96.34 seconds) on the telephone task time taken; (%); aspirin controls with MIs performed significantly (p=0.031) better than aspirin controls without MIs (mean 28.70 versus 27.71) on the MMSE; aspirin cases without MIs performed significantly (p=0.039) better than aspirin cases with MIs (mean 21.19 versus 27.33) on NART errors.

These findings are not consistent in that we would expect any significant differences to be found in similar neuropsychological tests for all proxies of CHD, and probably also within the same cognitive domains.

It is unlikely that these findings would affect the conclusions drawn from the age-adjusted comparisons of the five subgroups, since only telephone task time taken was significant for that analysis, where aspirin cases performed significantly worse than controls (not on aspirin or warfarin) and aspirin controls, and only controls (not on aspirin or warfarin) were significant for 'telephone time taken' when analysed here. In addition, some of the subgroups (particularly 'cases -not on aspirin or warfarin', n=25) contained very small samples, making interpretation difficult.

b) Diabetes

Mann-Whitney tests demonstrated no significant differences between those with and without diabetes for all five subgroups for most neuropsychological tests. The only exception to this was that cases (not on aspirin or warfarin) with diabetes performed significantly better than cases (not on aspirin or warfarin) without diabetes for: Logical Memory Immediate (raw) (p=0.007, mean 18.75 versus 11.67); Logical Memory Immediate (%) (p=0.007, mean 44.75 versus 14.81); Logical Memory Delayed (raw) (p=0.004, mean 18.25 versus 7.33); and Logical Memory Delayed (%) (p=0.004, mean 66.50 versus 25.90).

However, the numbers in this subgroup were very small, with only 4 cases (not on aspirin or warfarin) who had diabetes. This makes interpretation of these findings difficult. In addition, since there were no significant differences between subgroups when they were compared for cognitive function with adjustment for age only (on all tests except for telephone test time taken), it is unlikely that this would be affected by our finding of possibly better performance in the logical memory subtests for cases (not on aspirin or warfarin) with diabetes.

c) Hypertension

Mann-Whitney tests demonstrated no significant differences between those with and without hypertension for all five subgroups for all neuropsychological tests. The only exception to this was that warfarin cases without hypertension performed significantly (p=0.047) better than warfarin cases with hypertension, although the difference between actual mean scores was very small (18.54 versus 17.44). Therefore it is unlikely that hypertension confounds the relationship between subgroup and cognitive function.

d) Heart failure

Mann-Whitney tests demonstrated no significant differences between those with and without heart failure for all five subgroups for all neuropsychological tests. The only exception to this was that controls (not on aspirin or warfarin) without heart failure performed significantly (p=0.034) better than controls (not on aspirin or warfarin) with heart failure, with means of 29.73 versus 5.00. However, there were only two controls (not on aspirin or warfarin) with heart failure, therefore it is difficult to interpret these findings. Overall, it is unlikely that heart failure confounds the relationship between subgroup and cognitive function.

e) Duration of AF (cases only)

Spearman's correlations were performed to assess the relationship between duration of AF and cognitive function for the three subgroups. The only statistically significant correlation (p=0.021) was for warfarin cases, where there was a correlation with telephone task time taken. However, the correlation coefficient was small (Rho = 0.245).

Overall, duration of AF did not appear to confound the conclusions derived from the age-adjusted comparisons of the three subgroups.

f) Cholesterol

Spearman's correlations were performed to assess the relationship between cholesterol and cognitive function for the five subgroups. Most correlations were small and not significant. The few exceptions to this were: aspirin cases showed a correlation between cholesterol level and map search 2nd minute right score (p=0.001, Rho =0.460); aspirin controls showed a correlation between cholesterol level and total immediate raw score (p=0.042, Rho= -0.292); aspirin controls

showed a correlation between cholesterol level and Rey complex figure delayed score (p=0.017, Rho= -0.339); aspirin controls showed a correlation between cholesterol level and PASAT-2.4 seconds (p=0.033, Rho= -0.304); and cases (not on aspirin or warfarin) showed a correlation between cholesterol and Rey complex figure copy score (p=0.029, Rho = -0.501). The correlation coefficients were small and there was no consistent pattern across tests measuring the same domain or within one of the five subgroups.

Overall, there appears to be no effect of cholesterol level on the relationship between subgroup and cognitive function.

g) Health Status

Spearman's correlations were performed to assess the relationship between each of the SF-36 domains (physical functioning, role-physical, bodily pain, general health, vitality, role emotional, mental health) and each of the neuropsychological tests for all five subgroups. The majority of correlations for most of the neuropsychological tests for nearly all subgroups were not statistically significant. Despite a considerable number of statistically significant correlations (table 7.24), only a minority have a reasonably large correlation coefficient (Rho >+/- 0.4) implying a noteworthy correlation, and these are shown in table 7.24. Interpretation of these findings is difficult. Such correlations were present for: vitality with MMSE and PASAT-2.4 (cases - not on aspirin or warfarin); emotion with telephone task time taken (aspirin controls); mental health with logical memory immediate raw, immediate %, delayed raw (aspirin cases and controls); mental health with logical memory delayed % (aspirin controls); and mental health with Rey copy and telephone task decrement (cases - not on aspirin or warfarin). All of these correlations were in the same direction, such that the 'healthier' and 'happier' SF-36 score correlated with better cognitive function. It is therefore possible that the cognitive function of subgroups is weakly associated with

SF-36 score. However, since the great majority of correlations were very weak and non-significant (therefore not shown here), our findings here do not provide strong evidence for a confounding effect of health status on the relationship between subgroup and cognitive function at baseline.

Table 7.24: Spearman's correlation and p-values for subtests with significant (p <0.05) correlation between health status and cognitive function for subgroups. (2dp)

SF-36 domain	Subgroup	Neuropsychological Test	Spearman's Correlation Coefficient	p-value for Spearman's correlation
Vitality	Case - not on aspirin or warfarin	MMSE	0.42*	0.04
Vitality	Case - not on aspirin or warfarin	PASAT-2.4	0.42*	0.04
Emotion	Aspirin Control	Telephone Task Time Taken	-0.41*	0.002
Mental Health	Aspirin Case	Logical Memory Immediate (raw)	0.46*	0.00
Mental Health	Aspirin Case	Logical Memory Immediate (%)	0.45*	0.00
Mental Health	Aspirin Case	Logical Memory Delayed (raw)	0.44*	0.00
Mental Health	Aspirin Control	Logical Memory Immediate (raw)	0.49*	0.00
Mental Health	Aspirin Control	Logical Memory Immediate (%)	0.50*	0.00
Mental Health	Aspirin Control	Logical Memory Delayed (raw)	0.57*	0.00
Mental Health	Aspirin Control	Logical Memory Delayed (%)	0.47*	0.00
Mental Health	Aspirin Control	Telephone Task Time Taken	-0.55*	0.00
Mental Health	Aspirin Control	NART No. of Errors	-0.52*	0.00
Mental Health	Aspirin Control	NART Predicted IQ	0.44*	0.001
Mental Health	Aspirin Control	PASAT (2.4-seconds)	0.48*	0.00
Mental Health	Case - not on aspirin or warfarin	Rey Complex Figure Copy	0.42*	0.04
Mental Health	Case - not on aspirin or warfarin	Telephone Task Dual Task Decrement	-0.64*	0.001

*Rho > +/- 0.4

h) Education

Spearman's correlations were performed to assess the relationship between education ('age at leaving continuous full-time education) and cognitive function for the five subgroups. The majority were not significant. However, of the significant correlations, only those for NART errors and NART IQ (aspirin cases) were large enough to be noted (Rho > +/- 0.4). Only those which are were significant and of notable size are shown in table 7.25. Here, aspirin cases showed significant correlation between leaving school at an older age and performing better on this neuropsychological test. Since the remainder of subtests showed no noteworthy correlations however, these findings do not provide strong evidence to suggest that education confounds the relationship between subgroup and cognitive function.

Table 7.25: Spearman's correlation and p-values for subtest s with significant (p <0.05) correlation between education and cognitive function for subgroups. (2dp)

Subgroup	Neuropsychological Test	Spearman's Correlation Coefficient	p-value for Spearman's correlation
Aspirin Case	NART No. of Errors	-0.46*	0.00
Aspirin Case	NART Predicted IQ	0.45*	0.00

*Rho > +/- 0.4

Summary of subgroup confounder analysis

Assessment of key potential confounders (CHD, diabetes, hypertension, heart failure, cholesterol, and health status) through incorporation of the confounding variable into the model as a covariate demonstrated no strong evidence that any of the variables affected the conclusions derived from age-adjusted comparisons between subgroups of cases and controls on aspirin/ warfarin/ neither. This analysis was limited, however, by small subgroup samples (particularly cases not on aspirin or warfarin) which became even smaller once they were divided into those with and without potentially confounding variables.

Stratification according to stroke risk

1) Descriptive statistics

Descriptive statistics for stroke risk for the CAFÉ cohort according to SPAF[55,58,63,69] criteria are described in Table 7.26 and 7.27. Similar distributions of level of stroke risk were present for treatment subgroups. Since SPAF criteria are for assessing those with NVAF, only cases were included in this analysis.

Table 7.26: Stroke risk stratification in the CAFÉ cohort according to SPAF criteria (cases only)

Stroke risk	CAFÉ cohort % (all cases)
High risk	52.6
Intermediate risk	15.6
Low risk	31.8

Table 7.27: Stroke risk stratification in the CAFÉ cohort according to SPAF criteria (cases only - treatment subgroups)

Stroke Risk	CAFÉ cohort %		
	Aspirin Cases	Warfarin Cases	Cases (not on warfarin or aspirin)
High risk	56.7	44.3	68.0
Intermediate risk	11.7	19.3	12.0
Low risk	31.7	36.4	20.0

2) Comparison of neuropsychological test scores

ANOVA techniques were used to compare the mean neuropsychological test score at baseline according to stroke risk (Table 7.28). There were no significant differences in test score between those of high, intermediate and low stroke risk.

Therefore, interpreting these findings, there does not appear to be convincing evidence of a pattern suggesting a relationship between stroke risk (according to SPAF criteria) and performance on neuropsychological tests at baseline for cases in NVAF.

Table 7.28: Comparison of mean neuropsychological test score at baseline according to stroke risk (using SPAF criteria) for cases only (2dp)

Neuropsychological test	Mean test score according to stroke risk			P-value
	High risk	Intermediate risk	Low risk	
MMSE	28.66	28.22	28.22	0.21
Logical Memory (immediate, raw)	14.23	16.11	13.42	0.15
Logical Memory (immediate, %)	24.35	32.52	20.64	0.09
Logical Memory (delayed, raw)	10.47	12.07	10.71	0.56
Logical Memory (delayed, %)	35.85	42.41	33.84	0.34
Rey Complex (copy)	31.67	32.43	31.91	0.74
Rey Complex (delayed)	12.20	13.02	12.79	0.79
Map Search (1st Minute, Left)	15.89	15.67	16.07	0.98
Map Search (1st Minute, Right)	5.31	3.11	5.35	0.34
Map Search (2nd Minute, Left	9.48	8.85	8.75	0.82
Map Search (2nd Minute, Right)	8.90	8.37	8.71	0.96
Telephone Task No. of Targets	17.38	17.67	17.36	0.91
Telephone Task Time Taken	101.38	111.89	104.93	0.55
Telephone Task Dual Task Decrement	6.66	3.56	4.41	0.71
NART No. of Errors	21.41	19.74	23.96	0.16
NART Predicted IQ	104.22	106.19	101.09	0.18
Digit Span	13.18	14.15	13.85	0.34
PASAT (2.4-seconds)	29.75	28.22	30.02	0.89
PASAT (1.2-seconds)	12.55	13.78	10.11	0.36

Chapter 7 Summary

- When neuropsychological test means were compared for cases and controls and for subgroups on aspirin, warfarin and neither treatment, there were few significant differences when crude data was examined, nor after adjustment for age. Those differences which were statistically significant were predominantly small and did not suggest important clinically significant differences between groups.
- Key potential confounders were assessed in the total study population and there was little important association between these and performance on neuropsychological tests. In addition, the effect of key confounders (as covariates in the model) on the conclusions derived from age-adjusted comparisons between cases and controls and between subgroups was weak or absent, although the analysis of sub-groups was restricted by small numbers.
- Thus the issue of confounding has been thoroughly examined for the baseline results. Therefore confidence can be held in the principal findings that there is no apparent relationship between NVAF or treatment subgroup and performance on neuropsychological tests at baseline.
- When the results were stratified according to stroke risk (according to SPAF criteria) there was no convincing evidence of a pattern suggesting a relationship between stroke risk and performance on neuropsychological tests at baseline for cases in NVAF.

Chapter 8 - Results (III): Follow-up Results - Neuropsychological test battery scores

- Statistical Methods
- Characteristics of responders and non-responders
- Findings for the total study population
- Comparison between cases and controls
    - Findings for cases and controls analysed separately
    - Analysis by cognitive domain
    - Analysis comparing differences between cases and controls
- Comparison of sub-groups
- Correlations of repeated neuropsychological tests
- Examination of potential confounders
- Stratification according to stroke risk
- Chapter 8 Summary

Statistical methods used:

Data from baseline and 12-month follow-up interviews and GP notes was combined into a single SPSS database.

i) Responder / non-responder analyses.

Descriptive statistics (medians since data was non-parametric) were calculated to explore the relationship between those who completed the follow-up interview and those who only completed baseline interview. The significance of differences between the two groups was determined using Mann-Whitney nominal data and Pearson Chi-squared techniques as appropriate.

ii) Comparison of change in neuropsychological test scores over time, for total population and between cases and controls.

Firstly descriptive statistics were calculated for the change in performance on the neuropsychological tests for the total study population, incorporating both cases and controls. Comparisons were then made of the decline in cognitive function over 12 months, between cases and controls. In all calculations, 'change in test performance over the follow-up period' was the difference between an individual's score at follow-up and their score at baseline: -

- Due to the non-normal distribution of the data, non-parametric tests were used to compare baseline and follow-up neuropsychological test scores.
- When analysing the results for cases and controls, the change in performance over time was firstly analysed at an individual level ('within group' analyses, comparing an

individual's performance at 12 month follow-up to their own performance at baseline). The most useful way to demonstrate this was through graphical analyses.

- Analyses of the overall change in performance for each subtest were then undertaken for both cases and controls. 'Between group' analyses were performed comparing mean change in test performance over 12 months between cases and controls. Statistical significance of the change in performance was calculated using Wilcoxon Signed Rank Test because of the non-parametric nature of the data. This was applied to the difference between neuropsychological test scores at baseline and follow-up scores for cases and controls separately, in order to further investigate the statistical significance of change in performance over time for each group. One-sample t-tests were then performed to determine whether any differences noted using Wilcoxon signed rank were statistically significant.

- Differences (in change in performance over the follow-up period) between cases and controls were then analysed using Chi-squared tests, by comparing the proportion of cases and controls that improved, deteriorated and stayed the same.

iii) Comparison of change in neuropsychological test scores over time, between treatment subgroups.

Firstly descriptive statistics were calculated for the change in performance on the neuropsychological tests for treatment subgroups (cases on warfarin, cases on aspirin, cases on neither treatment, controls on aspirin and controls on neither). Again, in all calculations, 'change in test performance over the follow-up period' was the difference between an individual's score at follow-up and their score at baseline. The subgroups were then compared:-

- Analysis of the overall change in performance for each subtest was then undertaken for all treatment subgroups. Again, non-parametric tests were employed. Differences in change in performance over the follow-up period between the five treatment subgroups were compared using ANOVA techniques, with and without adjustment for age.

- Chi-squared tests were then used to compare the proportion of cases on aspirin/ warfarin/ neither who improved/ deteriorated/ stayed the same.

- In addition, since more than two groups were analysed, the Kruskal-Wallis test was used to further examine these differences, and again statistical significance was tested using the Mann-Whitney test for independent groups.

iv) Neuropsychological test correlations

In order to explore the extent of change over time for all neuropsychological tests for the total study population and for cases and controls, tests of correlation were used. An individual's

mean score at baseline was correlated against their own score at 12 month follow-up using Pearson's correlation techniques.

v) Effect of potential confounders

The effect of age and education on the change in performance on neuropsychological tests over the follow-up period was examined using a regression model (analysis of covariance general linear model) with age and education as covariates. In addition, Pearson's correlation techniques were used to explore the relationship between age at first interview and change in score over the follow-up period on each of the neuropsychological subtests for the whole study population. The other analyses presented in this chapter were undertaken using crude data, without adjustment for confounders.

vi) Stratification according to stroke risk

Cases only were stratified according to stroke risk (high, intermediate or low) according to SPAF criteria[55,58,63,69] as described in Chapter 2. ANOVA and post-hoc tests (including Bonferonni adjustments and linear regression) were then used to compare change in neuropsychological test score over time between those of different stroke risks.

Characteristics of responders and non-responders for follow-up interview:

Comparisons were made between participants included after baseline interview (n=362) who did and did not complete follow-up interview at 12 months (table 8.1). Responders were considered as those who were included following the baseline interview and also included after follow-up interview (n=305), non-responders were those who were included following baseline interview, but were not included at follow-up interview (n=57), either because they died (n=16), refused (n=24) or were too ill/ had other miscellaneous reasons for non-response (n=17). Comparison between these groups was possible for all variables which had been collected during GP notes screening, with key comparisons described here. The notes screening process had been designed with consideration of the likely need for these analyses

We found no significant differences between responders and non-responders for age, sex, education or documented co-morbidities (CHD, CHF, hypertension, diabetes, thyrotoxicosis, Parkinson's disease, peripheral vascular disease, depression), although the study was not powered specifically to explore these characteristics. The only significant differences found were that for the SF-36, those who had completed the follow-up visit had higher (better) baseline scores than those who were not followed up for the physical functioning (p=0.015), role-physical (p=0.043) and general health (p=0.020) domains.

Table 8.1: Characteristics of responders and non-responders (2dp)

Variable	Completed follow-up interview?		Total (n=361)	P-values for comparison of groups (using Mann-Whitney and Chi squared techniques)
	Yes (n=304)	No (n=57)		
Median age (years) – male	74.6	75.7	75.0	0.11
Median age (years) - female	78.2	74.4	77.9	0.20
Median age (years) - total	76.1	75.6	75.8	0.83
Coronary Heart Disease (%)	36.5	40.4	37.1	0.58
Heart Failure (%)	5.9	10.5	6.6	0.20
Hypertension (%)	36.5	49.1	38.5	0.07
Diabetes (%)	9.9	12.3	10.2	0.58
Thyrotoxicosis (%)	1.6	3.5	1.9	0.35
Parkinson's Disease (%)	0.7	0.0	0.6	0.54
Peripheral Vascular Disease (%)	7.5	8.7	7.7	0.79
Depression (past history) (%)	10.5	7.0	10.0	0.42
Depression (current) (%)	3.0	1.8	2.8	0.61
Ever taken aspirin (%)	46.4	50.9	47.1	0.53
Ever taken warfarin (%)	24.3	26.3	24.7	0.75
Left school at 14 years or under (%)	65.4	68.4	65.9	0.75
No school qualifications	71.1	70.2	70.9	0.76
Case status of those who completed follow-up – (% cases)	46.7	56.1	48.2	0.19
Daily smokers (%)	11.2	15.8	11.9	0.54
Daily drinkers (%)	19.1	26.3	20.2	0.33
SF-36 Physical activity (mean score)	65	60	65	0.02*
SF-36 Role- physical (median score)	75	50	75	0.04*
SF-36 Pain (median score)	60	50	75	0.09
SF-36 General health (median score)	65	55	60	0.02*
SF-36 Vitality (median score)	70	65	65	0.11
SF-36 Emotion (median score)	100	100	100	0.60
SF-36 Mental Health (median score)	72	72	72	0.26

* $p<0.05$

Findings for the total study population

Change in performance on the neuropsychological tests between baseline and follow-up was not significant for most tests (table 8.2) when the total study population (cases and controls) was analysed without stratification. Only Map search 1st minute right showed significant change over the follow-up period. The direction of this change was improvement, supporting an explanation that this may be due to practice effects (as described in Chapter 4), and this is particularly feasible considering that this is the first of the map search tasks. The lack of any significant change in the other three components of the map search subtest also reduces the likelihood that this finding is due to clinically significant cognitive change. Overall there is no strong evidence to suggest a significant change in performance over time when the total study population is analysed as a whole.

Table 8.2: Change in performance over time for the total population (2dp)

	Mean (Baseline)	Mean (f/u)	Mean Difference (baseline – f/u †)	p-value (using Mann-Whitney)
MMSE	28.40	28.49	-0.09	0.94
Logical Memory Immediate (raw)	14.81	15.78	-1.02	0.92
Logical Memory Immediate (%)	25.82	29.74	-4.11	0.70
Logical Memory Delayed (raw)	10.96	11.28	-0.41	0.13
Logical Memory Delayed (%)	36.98	39.67	-2.98	0.06

	Mean (Baseline)	Mean (f/u)	Mean Difference (baseline – f/u †)	p-value (using Mann-Whitney)
Rey Complex Figure Copy	31.83	30.32	1.50	0.64
Rey Complex Figure Delayed	13.16	12.26	0.89	0.53
Map Search (1st Minute, Left)	16.83	17.66	-0.67	0.02*
Map Search (1st Minute, Right)	5.25	5.46	-0.24	0.70
Map Search (2nd Minute, Left	9.60	7.77	1.85	0.18
Map Search (2nd Minute, Right)	9.20	10.25	-0.93	0.20
Telephone Task No. of Targets	17.45	17.85	-0.44	0.93
Telephone Task Time Taken	98.48	94.43	4.31	0.69
Telephone Task Dual Task Decrement	4.38	3.03	1.30	0.70
NART No. of Errors	21.50	23.11	-1.73	0.46
NART Predicted IQ	103.67	102.00	1.90	0.37
Digit Span	13.76	13.24	0.47	0.83
PASAT (2.4-seconds)	30.05	27.60	2.49	0.97
PASAT (1.2-seconds)	12.63	8.50	4.15	0.49

* $p<0.05$

† mean differences in scores for individuals were analysed first, then the mean of these mean differences was calculated

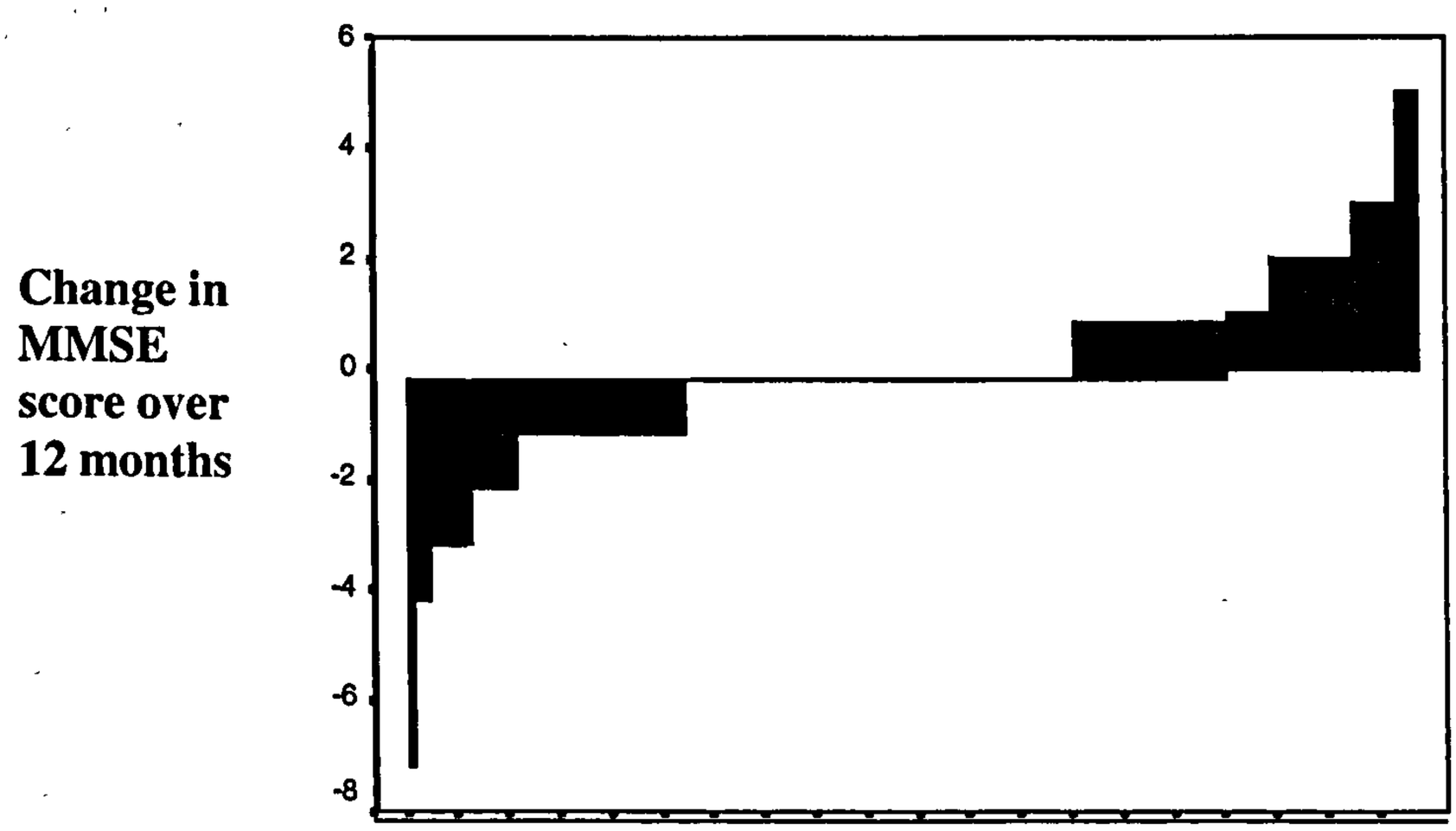
Comparison of cases and controls

1. Findings for cases and controls analysed separately

i) Analysis of change over time in individuals

Firstly, at an individual level, change in performance over the follow-up period varied between individuals, in that for each sub-test, some individuals improved and some deteriorated. This is demonstrated visually in figure 8.1. Similar patterns were shown for all sub-tests, i.e. similar proportions of the population demonstrating improvement and deterioration; although the proportion of participants showing no change varied between sub-tests, being greatest for the MMSE and least for map search task 1st minute left. This suggests, as discussed in Chapter 4, that sensitivity of the tests to detect change in performance over time may vary between sub-tests, or that the subtests measure different cognitive domains, as expected. Alternatively, the variation between tests may be due to chance, and further analyses below explore this possibility.

Fig 8.1. Chart to show summary of MMSE scores changes for individuals over follow-up period



ii) Analysis of change over time in the population

Next, population differences were explored. The overall direction of change in test scores over the follow-up period was analysed and is described below. This varied widely for both cases and controls, in that for both groups, there was an overall improvement in some sub-tests and deterioration in others. However, the change in test score was only statistically significant ($p<0.05$) for a proportion of the tests:-

a) Cases

When Wilcoxon Signed Rank techniques were used (table 8.3), the mean difference between mean score at baseline and mean score at follow-up was statistically significant for: logical memory immediate (raw and %), Rey complex figure copy, NART (errors and IQ) and PASAT (1.2 seconds).

Of these statistically significant test results, two subtests (logical memory immediate raw and %) showed improvement over the follow-up period, whilst four tests (Rey copy, NART errors, NART IQ and PASAT-1.2 seconds) showed deterioration over the follow-up period.

Table 8.3: Wilcoxon Signed Rank Test applied to the difference between neuropsychological test scores at baseline and follow-up for cases (2dp)

Neuropsychological test	No. (negative rank)	No. (positive rank)	No. (ties)	Direction of change (follow-up minus baseline)	Predominant direction
MMSE	38	47	53	No. improving > No. deteriorating	Improvement p=0.37
Logical memory test (immediate, raw)	52	70	16	No. improving > No. deteriorating	Improvement *p=0.01
Logical memory test (immediate, %)	51	69	17	No. improving > No. deteriorating	Improvement *p=0.04
Logical memory test (delayed, raw)	61	62	15	No. improving > No. deteriorating	Improvement p=0.98
Logical memory test (delayed, %)	59	64	14	No. improving > No. deteriorating	Improvement p=0.60
Rey (copy)	73	41	24	No. deteriorating > No. improving	Deterioration *p=0.00
Rey (recall)	65	65	8	No. deteriorating = No. improving	Stays same p=0.20
Map (left, 1st minute)	67	61	7	No. deteriorating > No. improving	Deterioration p=0.47
Map (right, 1st minute)	42	49	44	No. improving > No. deteriorating	Improvement p=0.54
Map (left, 2nd minute)	67	58	10	No. deteriorating >No. improving	Deterioration p=0.18

Neuropsychological test	No. (negative rank)	No. (positive rank)	No. (ties)	Direction of change (follow-up minus baseline)	Predominant direction
Map (right, 2nd minute)	64	58	13	No. deteriorating > No. improving	Deterioration p=0.77
Telephone task (no. of targets)	54	51	32	No. deteriorating > No. improving	Deterioration p=0.69
Telephone task (time taken)	73	62	2	No. improving > No. deteriorating	Improvement p=0.22
Telephone task (dual task decrement)	72	60	2	No. improving > No. deteriorating	Improvement p=0.19
NART (no. of errors)	37	88	13	No. deteriorating > No. improving	Deterioration *p=0.00
NART (IQ)	87	36	13	No. deteriorating > No. improving	Deterioration *p=0.00
Digit span	71	49	17	No. deteriorating > No. improving	Deterioration p=0.06
PASAT (2.4-seconds)	71	57	7	No. deteriorating > No. improving	Deterioration p=0.08
PASAT (1.2-seconds)	65	31	40	No. deteriorating > No. improving	Deterioration *p=0.00

*p<0.05

b) Controls

When Wilcoxon Signed Rank techniques were used (table 8.4), the mean difference between mean score at baseline and mean score at follow-up was statistically significant ($p<0.05$) for the same sub-tests as for cases: logical memory immediate (raw and %), Rey complex figure copy, NART (errors and IQ), digit span and PASAT (1.2 seconds); but also showed significant change in Rey complex figure delayed, map search (1st minute left, 2nd minute left and 2nd minute right), telephone task (time taken and dual task decrement) and PASAT (2.4 seconds).

For controls, of the statistically significant test results, eight tests (logical memory immediate raw, logical memory immediate %, logical memory delayed raw, logical memory delayed %, map left 1st minute, map right second minute, telephone time taken, telephone dual task decrement) showed improvement over the follow-up period, and eight tests (Rey copy, Rey recall, map left 2nd minute, NART errors, NART IQ, Digit span, PASAT-2.4 seconds, PASAT-1.2 seconds) demonstrated deterioration.

Table 8.4: Wilcoxon Signed Rank Test applied to the difference between neuropsychological test scores at baseline and follow-up for controls (2dp)

Neuropsychological test	No. (negative rank)	No. (positive rank)	No. (ties)	Direction of change (follow-up minus baseline)	Predominant direction
MMSE	45	57	54	No. improving > No. deteriorating	Improvement p=0.42
Logical memory test (immediate, raw)	56	82	18	No. improving > No. deteriorating	Improvement *p=0.03
Logical memory test (immediate, %)	55	79	22	No. improving > No. deteriorating	Improvement *p=0.03
Logical memory test (delayed, raw)	54	80	22	No. improving > No. deteriorating	Improvement *p=0.03
Logical memory test (delayed, %)	52	83	21	No. improving > No. deteriorating	Improvement *p=0.002
Rey (copy)	82	50	24	No. deteriorating > No. improving	Deterioration *p=0.002
Rey (recall)	83	66	70	No. deteriorating >No. improving	Deterioration *p=0.02
Map (left, 1st minute)	58	87	11	No. improving > No. deteriorating	Improvement *p=0.01
Map (right, 1st minute)	51	55	50	No. improving > No. deteriorating	Improvement p=0.997
Map (left, 2nd minute)	89	53	14	No. deteriorating > No. improving	Deterioration *p=0.00

Neuropsychological test	No. (negative rank)	No. (positive rank)	No. (ties)	Direction of change (follow-up minus baseline)	Predominant direction
Map (right, 2nd minute)	52	85	19	No. improving > No. deteriorating	Improvement *p=0.03
Telephone task (no. of targets)	62	58	34	No. deteriorating > No. improving	Deterioration p=0.86
Telephone task (time taken)	82	66	6	No. improving > No. deteriorating	Improvement *p=0.02
Telephone task (dual task decrement)	93	58	2	No. improving > No. deteriorating	Improvement *p=0.03
NART (no. of errors)	42	94	17	No. deteriorating > No. improving	Deterioration *p=0.00
NART (IQ)	93	42	17	No. deteriorating > No. improving	Deterioration *p=0.00
Digit span	72	51	32	No. deteriorating > No. improving	Deterioration *p=0.008
PASAT (2.4-seconds)	82	64	10	No. deteriorating > No. improving	Deterioration *p=0.06
PASAT (1.2-seconds)	67	41	46	No. deteriorating > No. improving	Deterioration *p=0.001

*p = statistically significant (p<0.05)

c) Summary of findings for cases and controls analysed separately

When the overall change in performance on neuropsychological test was analysed for cases, a statistically significant ($p<0.05$) overall improvement was found in two subtests, with deterioration in four subtests. Controls showed improvement and deterioration in the same sub-tests as for cases, but also showed improvement in a further six subtests and deterioration in a further four subtests (table 8.5). Therefore, although the overall pattern is of improvement in more subtests in controls than cases, there is also deterioration in more subtests in controls than cases; this is not consistent with the expected effect of AF on cognitive decline, and these findings are not consistent with an overall deterioration in performance associated with NVAF.

Table 8.5: Significant changes in scores based on Wilcoxon Rank Sum analysis - cases and controls

	Direction of change in score of neuropsychological subtests			
	Significant* improvement in scores		**Significant* deterioration in scores**	
	Neuropsychological test	**p-value**	**Neuropsychological test**	**p-value**
Cases	a) Logical memory test (immediate, raw)	0.010*	a) Rey (copy)	<0.001*
	b) Logical memory test (immediate, %)	<0.001*	b) NART (errors)	<0.001*
			c) NART (IQ)	<0.001*
			d) PASAT (1.2-seconds)	<0.001*
Controls	a) Logical memory test (immediate, raw)	0.03*	a) Rey (copy)	0.002*
	b) Logical memory test (immediate, %)	0.03*	b) NART (errors)	<0.001*
	c) Logical memory test (delayed, raw)	0.033*	c) NART (IQ)	<0.001*
	d) Logical memory test (delayed, %)	0.002*	d) PASAT (1.2-secs)	0.001*
	e) Map (left, 1st minute)	0.011*	e) Rey (recall)	0.015*
	f) Map (right, 2nd minute)	0.026*	f) Map (left, 2nd minute)	<0.001*
	g) Telephone task (time taken)	0.018*	g) Digit span	0.008*
	h) Telephone task (dual task decrement)	0.025*	h) PASAT (2.4-secs)	0.059*

*p = statistically significant (p<0.05)

2. *Analysis by cognitive domain*

Subtests which measured the same cognitive domain were grouped together (table 8.6). The overall direction of change (i.e. whether there was improvement or deterioration over the follow-up period) varied between subtests which assessed the same cognitive domain. Any change in performance would be expected to be cognitive domain-specific and represented in all tests evaluating that domain (see chapter 5). In addition, as with previous analyses, most changes in performance over the follow-up period were not statistically significant.

Table 8.6: Analysis of change in test scores by cognitive domain

Cognitive Domain		Neuropsychological test	Improvement or deterioration?	
			Cases	Controls
Memory	Verbal short-term	Logical immediate raw	Improvement	Improvement
		Logical immediate %	Improvement	Improvement
		Logical delayed raw	NS	Improvement
		Logical delayed %	NS	Improvement
		Digit span subtest	NS	Deterioration
	Non-verbal	Rey complex copy	Deterioration	Deterioration
		Rey complex delayed	NS	Deterioration
Attention	Selective	Map search test 1st min rt.	NS	Improvement
		Map search test 1st min lt.	NS	NS
		Map search test 2nd min rt.	NS	Deterioration
		Map search test 2nd min lt.	NS	Improvement
		Telephone task no. targets	NS	NS
		Telephone task time taken	NS	Improvement
	Divided/ Sustained	Telephone dual task decrement	NS	Improvement
	General	PASAT –1.2 seconds	NS	Deterioration
		PASAT –2.4 seconds	Deterioration	Deterioration
Premorbid Intelligence		NART errors	Deterioration	Deterioration
		NART IQ	Deterioration	Deterioration
General cognitive function		MMSE	NS	NS
Information processing		PASAT –1.2 seconds	NS	Deterioration
		PASAT –2.4 seconds	Deterioration	Deterioration

NS = not significant ($p>0.05$)

3. Analysis comparing differences between cases and controls

The difference between change in test score over the follow-up period for cases and controls was analysed using Chi squared techniques (table 8.7). There were no statistically significant differences between the proportion of cases and controls that improved, deteriorated or stayed the same for each subtest over the 12-month follow-up period. This suggests that there is no meaningful difference in change in performance on neuropsychological tests between cases and controls.

Table 8.7: Difference between change in test score of cases and controls

Neuropsychological test	Mean Difference (SD) in performance over follow-up period (baseline – f/u)		Chi- squared statistic (p-value) for difference between cases and controls
	Cases	Controls	
MMSE	0.10	-0.07	0.46 (0.79)
Logical Memory Immediate (raw)	-1.01	-1.05	0.11 (0.95)
Logical Memory Immediate (%)	-3.86	-4.32	0.27 (0.89)
Logical Memory Delayed (raw)	0.03	-0.80	2.94 (0.23)
Logical Memory Delayed (%)	-0.89	-4.81	3.08 (0.22)
Rey Complex Figure Copy	1.70	1.32	0.31 (0.86)
Rey Complex Figure Delayed	0.66	1.09	1.17 (0.56)
Map Search (1st Minute, Left)	0.76	-1.91	4.61 (0.10)
Map Search (1st Minute, Right)	-0.55	0.03	0.09 (0.96)
Map Search (2nd Minute, Left	1.04	2.56	2.49 (0.29)

	Mean Difference (SD) in performance over follow-up period (baseline – f/u)		
	Cases	**Controls**	
Map Search (2nd Minute, Right)	-0.31	-1.47	6.0 (0.50)
Telephone Task No. of Targets	-0.088	-0.75	0.7 (0.97)
Telephone Task Time Taken	3.86	4.71	1.70 (0.44)
Telephone Task Dual Task Decrement	2.99	-0.19	1.46 (0.48)
NART No. of Errors	-1.69	-1.76	0.28 (0.87)
NART Predicted IQ	2.63	1.25	0.31 (0.86)
Digit Span	0.34	0.59	3.54 (0.17)
PASAT (2.4-seconds)	2.60	2.39	0.22 (0.90)
PASAT (1.2-seconds)	4.61	3.74	1.02 (0.60)

Analysis of subgroups according to antithrombotic therapy

Chi-squared tests (table 8.8) showed no statistically significant differences in most neuropsychological test scores, between cases on aspirin, warfarin or neither treatment. The one exception was for the performance on PASAT-2.4 seconds for cases only, where more cases on aspirin deteriorated than improved, whilst equal numbers of cases on warfarin/ neither improved nor deteriorated.

The Kruskal-Wallis test was used to examine the differences in performance on neuropsychological test between all five subgroups (table 8.9), and showed no significant changes for any test over the test period, except for map search 1st minute left (p=0.037). Examining the rank data for this subtest, the greatest change in performance over time was for aspirin cases, and the least was for controls on neither aspirin or warfarin. Overall, there is no strong evidence for an association between treatment subgroup and cognitive decline.

Table 8.8: Differences in change in test score between treatment subgroups

Neuropsyc. test	Mean Difference in performance over follow-up period (baseline – f/u) (2dp)					Chi- squared statistic (p-value) for difference between treatment subgroups
	Aspirin cases	Warfarin cases	Aspirin controls	Controls – not on asp. or warf.	Cases - not on asp. or warf.	
MMSE	-0.21	-0.24	-0.04	-0.08	-0.65	13.2 (0.10)
Logical Memory Immediate (raw)	-1.04	-1.41	-1.16	-1.01	0.50	4.6 (0.33)
Logical Memory Immediate (%)	-5.61	-4.49	-6.05	-3.67	2.45	2.9 (0.58)
Logical Memory Delayed (raw)	-0.42	0.00	-0.86	-0.75	1.20	1.75 (0.78)
Logical Memory Delayed (%)	-2.91	-0.74	-3.91	-5.16	3.35	1.6 (0.81)

Neuropsyc. test	Mean Difference in performance over follow-up period (baseline – f/u)					Chi- squared statistic (p-value) for difference between treatment subgroups
	Aspirin cases	Warfarin cases	Aspirin controls	Controls – not on asp. or warf.	Cases - not on asp. or warf.	
Rey Complex Figure Copy	1.48	1.89	3.00	0.65	1.55	4.65 (0.33)
Rey Complex Figure Delayed	1.13	0.49	0.84	1.20	0.20	1.60 (0.81)
Map Search (1st Minute, Left)	2.89	-0.51	-0.68	-2.65	0.60	5.50 (0.24)
Map Search (1st Minute, Right)	-0.68	-0.90	-0.34	0.32	1.00	2.72 (0.61)
Map Search (2nd Minute, Left	0.18	1.38	4.23	2.08	1.70	0.76 (0.94)
Map Search (2nd Minute, Right)	1.36	-0.90	-1.27	-1.77	-1.90	3.13 (0.54)
Telephone Task No. of Targets	-0.65	0.25	-2.67	-0.13	0.00	10.6 (0.32)
Telephone Task Time Taken	3.99	5.23	0.77	6.12	-1.25	5.8 (0.22)
Telephone Task Dual Task Decrement	6.36	1.12	-1.09	0.19	2.36	4.91 (0.30)
NART No. of Errors	-1.49	-2.48	-1.00	-2.00	0.65	3.74 (0.44)
NART Predicted IQ	1.85	3.24	0.07	1.61	2.32	3.84 (0.43)
Digit Span	-0.30	0.56	0.68	0.4954	1.05	6.95 (0.14)
PASAT (2.4-seconds)	6.11	0.27	4.61	1.5727	3.00	15.0 (0.005*)
PASAT (1.2-seconds)	3.47	5.59	2.80	4.3241	3.75	5.60 (0.23)

*p = statistically significant (p<0.05

Table 8.9: Rank of differences in change in test score between treatment subgroups using Kruksall-Wallis Test

Neuropsyc. test	Mean rank for difference in performance over follow-up period					p-value for difference between treatment subgroups (2dp)
	Aspirin cases	Warfarin cases	Aspirin controls	Controls – not on asp. or warf.	Cases - not on asp. or warf.	
MMSE	144.70	157.13	149.26	145.95	109.97	0.26
Logical Memory Immediate (raw)	153.27	135.41	144.34	146.62	174.05	0.45
Logical Memory Immediate (%)	148.03	140.29	142.10	144.95	175.57	0.57
Logical Memory Delayed (raw)	145.96	155.60	142.20	138.60	168.27	0.52
Logical Memory Delayed (%)	145.72	158.60	143.25	135.07	168.73	0.29
Rey Complex Figure Copy	143.22	155.18	166.67	135.17	141.32	0.25
Rey Complex Figure Delayed	149.29	140.42	144.16	151.63	138.48	0.9
Map Search (1st Minute, Left)	173.61	146.85	146.44	128.72	161.85	0.04*
Map Search (1st Minute, Right)	141.92	141.41	139.95	149.80	149.23	0.94
Map Search (2nd Minute, Left	136.69	137.85	166.33	145.57	138.60	0.41
Map Search (2nd Minute, Right)	168.01	146.69	144.65	136.28	137.10	0.31
Telephone Task No. of Targets	126.79	156.37	129.50	149.67	154.35	0.22
Telephone Task Time Taken	133.33	153.07	135.42	151.12	130.45	0.51
Telephone Task Dual Task Decrement	133.90	141.92	129.64	151.21	150.77	0.57
NART No. of Errors	147.68	133.33	148.93	148.92	150.52	0.76
NART Predicted IQ	139.62	155.57	136.83	139.60	145.42	0.71
Digit Span	125.35	150.52	151.15	143.77	171.07	0.28

Neuropsyc. test	Mean rank for difference in performance over follow-up period					p-value for difference between treatment subgroups (2dp)
	Aspirin cases	Warfarin cases	Aspirin controls	Controls – not on asp. or warf.	Cases - not on asp. or warf.	
PASAT (2.4-seconds)	164.12	133.91	154.56	141.75	145.48	0.37
PASAT (1.2-seconds)	142.74	150.97	137.02	143.14	142.40	0.93

*p = statistically significant (p<0.05)

Correlations of repeated neuropsychological tests

Pearson's correlations of the scores at baseline and follow-up for each of the neuropsychological tests (cases and controls) are shown in table 8.10. For nearly all subtests, there was a highly significant correlation ($p<0.01$) between test score at baseline and test score at 12-month follow-up. The exceptions to this, where the correlation between score at baseline and score at follow-up was not significant, were map search test (1st minute right, 2nd minute left, 2nd minute right) for cases, and telephone task no. of targets for controls.

These findings suggest that there is very little correlation between extent of change in score over time for both cases and controls, for the majority of neuropsychological tests in the CAFÉ battery.

Table 8.10: Correlations of test scores at baseline and 12-month follow-up (2dp)

Neuropsychological test	Cases		Controls	
	Pearson's correlation coefficient	p-value	Pearson's correlation coefficient	p-value
MMSE	0.60	0.00*	0.54	0.00*
Logical Memory Immediate (raw)	0.72	0.00*	0.78	0.00*
Logical Memory Immediate (%)	0.63	0.00*	0.71	0.00*
Logical Memory Delayed (raw)	0.71	0.00*	0.75	0.00*
Logical Memory Delayed (%)	0.69	0.00*	0.69	0.00*
Rey Complex Figure Copy	0.53	0.00*	0.41	0.00*
Rey Complex Figure Delayed	0.63	0.00*	0.74	0.00*
Map Search (1st Minute, Left)	0.21	0.00*	0.39	0.00*
Map Search (1st Minute, Right)	0.16	0.07	0.30	0.00*
Map Search (2nd Minute, Left	0.03	0.71	0.22	0.01*
Map Search (2nd Minute, Right)	0.13	0.14	0.49	0.00*
Telephone Task No. of Targets	0.41	0.00*	-0.15	0.06
Telephone Task Time Taken	0.58	0.00*	0.48	0.00*
Telephone Task Dual Task Decrement	0.22	0.01*	0.67	0.00*
NART No. of Errors	-0.81	0.00*	-0.68	0.00*
NART Predicted IQ	0.89	0.00*	0.75	0.00*
Digit Span	0.71	0.00*	0.72	0.00*
PASAT (2.4-seconds)	0.64	0.00*	0.74	0.00*
PASAT (1.2-seconds)	0.55	0.00*	0.51	0.00*

*p = statistically significant ($p<0.05$)

Potential impact of confounders

Because this is a longitudinal study, many potentially confounding factors are removed because comparisons are made between an individual at follow-up and themselves at baseline. In addition, most relevant characteristics (for example comorbidities such as history of CHD) were unlikely to change over this time. Therefore, the collection of data on potential confounders was more extensive at baseline that at follow-up. Nevertheless, it is important to recognise the limitations of this reliance on baseline data, and that some characteristics may change over the follow-up period. Therefore it was felt appropriate to explore certain key variables in the follow-up data - these had been identified in literature searches and following the baseline confounder analysis:

1. Congestive Heart Failure (CHF)

The prevalence of proxy variables for CHF was examined to see whether they changed over the follow-up period. The only proxy variables available at both baseline and follow-up interviews were 'current symptom of ankle swelling – yes or no?', and 'current symptom of shortness of breath – none, yes but no effect, slight, marked or severe?'.

- For ankle swelling, 77% of participants at follow-up gave the same response as at baseline.

- For shortness of breath, 52% of participants gave an identical response to that given at baseline. When the answers were grouped as either 'no shortness of breath' or 'slight shortness of breath', and 'marked' or 'severe shortness of breath', 89% of participants gave the same response as at baseline.

Since the consistency of these responses over the follow-up period was reasonable, given the subjective nature of the variable, it was felt that CHF would have been unlikely to confound the results and therefore no further analysis was undertaken on these variables.

2. Age

Age did not confound the results when put into a general linear regression model. In addition, Pearson's correlation techniques (table 8.11) showed little relationship between age (at first interview) of the total population and change in neuropsychological test score over the follow-up period, except for a statistically significant but extremely small correlation between age and Rey copy, digit span and PASAT- 1.2 seconds. However, even these slight effects appeared insignificant when the analyses were checked graphically.

The effect of age on the change in cognitive performance over the follow-up period was examined because of the observed effect of age on the baseline results. However, it is clear that any effect of age on change in cognitive performance over the follow-up period will be almost identical for all participants since the follow-up period, thus the change in age, for all was very similar.

These findings suggest that it is unlikely that age confounds the results of change in cognitive performance over the follow-up period.

Table 8.11. Pearson's correlation for age and change in neuropsychological test score over the follow-up period (2dp)

Neuropsychological test	Pearson's Correlation Coefficient	p-value
MMSE	0.04	0.45
Logical Memory Immediate (raw)	0.04	0.50
Logical Memory Immediate (%)	0.01	0.92
Logical Memory Delayed (raw)	-0.04	0.54
Logical Memory Delayed (%)	-0.01	0.91
Rey Complex Figure Copy	0.14	0.02*
Rey Complex Figure Delayed	0.06	0.32
Map Search (1st Minute, Left)	0.10	0.08
Map Search (1st Minute, Right)	-0.02	0.71
Map Search (2nd Minute, Left	-0.01	0.89
Map Search (2nd Minute, Right)	-0.002	0.98
Telephone Task No. of Targets	-0.04	0.54
Telephone Task Time Taken	-0.09	0.12
Telephone Task Dual Task Decrement	0.09	0.12
NART No. of Errors	-0.003	0.96
NART Predicted IQ	0.07	0.26
Digit Span	-0.14	0.02*
PASAT (2.4-seconds)	0.09	0.14
PASAT (1.2-seconds)	0.15	0.01*

*p = statistically significant (p<0.05)

3. Educational level

Educational level did not confound the results when put into a general linear regression model. The analysis of the effect of this variable on follow-up data was performed because of the suggestion of a possible confounding effect at baseline. However, it is highly unlikely that educational level would change over the follow-up period in a cohort of elderly people, therefore any potential confounding effect would be extremely small.

4. Change in treatment over the follow-up period

Since this was an observational rather than an interventional study, it was not possible to control treatment of participants over the follow-up period. However, exploration of the possibility of an individual's treatment with antithrombotic therapy was important since GPs involved in the study may have been influenced by their practice's participation in the study and treatment of patients may have been reviewed as a result. In addition, other factors (e.g. guidelines and targets) may have led to changes in treatment of individuals.

Of 362 participants at baseline, four changed from aspirin to warfarin over the follow-up period, 13 started aspirin (previously on neither aspirin nor warfarin), three started warfarin (previously on neither aspirin nor warfarin) one stopped taking warfarin (and did not start aspirin) and two stopped taking aspirin (and did not start warfarin). These changes were too small to impact upon the findings of the 12-month follow-up. Therefore, it was decided that all analyses should be made according to the treatment subgroup of the participants at baseline.

Stratification according to stroke risk

One-way ANOVA tests were performed to compare the change in performance on neuropsychological tests between those of different stroke risk (Table 8.12), and post-hoc tests including Bonferroni adjustments were used to explore these findings further. Of these comparisons, only three showed a statistically significant difference between the change in performance of those of different stroke risks. These were Logical Memory (immediate raw, p=0.001), Logical Memory (immediate %, p=0.038) and Map Search (1st minute right, p=0.045). Analysing these three tests further: 1) those of intermediate stroke risk had significantly different changes in performances than those of low stroke risk for Logical Memory (immediate raw, p=0.004), Logical Memory (immediate %, p=0.047) and Map Search (1st minute right, p=0.020); 2) those of high stroke risk had significantly different change in performance than those of intermediate stroke risk for Logical Memory (immediate raw, p=0.041) and Map Search (1st minute right, p=0.027). (Note: equal variance were not assumed when calculating these p-values).

Interpretation of these findings is difficult, but overall there does not appear to be a consistent relationship between stroke risk and change in performance on neuropsychological tests over the follow-up period.

Table 8.12: Comparison of mean change in neuropsychological test score over the follow-up period according to stroke risk (using SPAF criteria) (2dp)

Neuropsychological test	Mean change in test score over follow-up period according to stroke risk			P-value
	High risk	Intermediate risk	Low risk	
MMSE	-0.01	0.50	0.11	0.46
Logical Memory (immediate, raw)	-0.97	1.77	-2.39	0.001*
Logical Memory (immediate, %)	-4.48	5.45	-7.49	0.04*
Logical Memory (delayed, raw)	-0.14	1.13	-0.24	0.48
Logical Memory (delayed, %)	-2.06	3.77	-1.40	0.43
Rey Complex (copy)	2.07	1.32	1.43	0.76
Rey Complex (delayed)	0.71	0.25	0.86	0.91
Map Search (1st Minute, Left)	0.90	3.57	-0.76	0.34
Map Search (1st Minute, Right)	0.10	-5.19	0.62	0.05*
Map Search (2nd Minute, Left	1.19	0.43	1.09	0.95
Map Search (2nd Minute, Right)	-0.99	1.10	0.07	0.71
Telephone Task No. of Targets	0.23	0.09	-0.65	0.39
Telephone Task Time Taken	-1.23	14.60	6.37	0.21
Telephone Task Dual Task Decrement	3.92	1.27	2.42	0.88
NART No. of Errors	-1.70	-1.60	-1.72	0.997
NART Predicted IQ	3.13	1.95	2.20	0.61
Digit Span	0.43	-0.32	0.61	0.37
PASAT (2.4-seconds)	3.81	2.29	1.07	0.65
PASAT (1.2-seconds)	5.82	7.90	1.33	0.05

*P<0.05

Chapter 8 Summary

- The only significant differences between those who did and did not complete the follow-up interview were that those who completed the follow-up had better baseline scores for the physical activity and general health domains of the SF-36.
- When the total study population was analysed without stratification, change in performance on the neuropsychological tests between baseline and follow-up was not significant for most tests.
- When cases and controls were analysed separately, the overall direction of change in test scores over the follow-up period varied widely, in that for both groups, there was an overall improvement in some sub-tests and deterioration in others. However, the change in test score was only statistically significant ($p<0.05$) for a proportion of the tests: cases demonstrated overall improvement in two subtests and deterioration in four subtests; controls showed improvement and deterioration in the same sub-tests as for cases, but also showed improvement in a further six subtests and deterioration in a further four subtests. These findings are not consistent with an overall deterioration in performance on neuropsychological testing in atrial fibrillation compared to sinus rhythm, and thus support the null hypothesis that there is no consistent association between NVAF and cognitive decline over 12 months.
- The overall direction of change (improvement or deterioration) varied between subtests which assessed the same cognitive domain.
- There were no statistically significant differences between the proportion of cases and controls that improved, deteriorated or stayed the same for each subtest over the 12-month follow-up period.
- There were no statistically significant differences in most neuropsychological test scores, between cases and controls on aspirin, warfarin or neither therapy.

- For nearly all subtests in the CAFE neuropsychological test battery, there was a highly significant correlation ($p<0.01$) between test score at baseline and test score at 12 month follow-up, suggesting very similar scores at baseline and score at follow-up for both cases and controls (for the majority of neuropsychological tests in the CAFÉ battery).
- Age and education did not confound the results when put into a regression model. In addition, Pearson's correlation techniques showed little relationship between age at baseline interview of the total population and change in the majority of neuropsychological test scores over the follow-up period.
- The number of participants who changed treatment subgroup according to antithrombotic therapy was small and did not impact upon the findings of the study.
- There did not appear to be a consistent relationship between stroke risk (according to SPAF criteria) and change in performance on neuropsychological tests over the follow-up period.
- Overall, these results demonstrate no consistent or significant change in cognitive performance over the 12-month period for the total study population, and no consistent or significant difference in change in cognitive performance between cases and controls, nor between treatment subgroups. These findings support the null hypothesis that decline in cognitive function over time (12 months) in people with NVAF is no different to that of controls.

Chapter 9 – Discussion

- Summary of findings
- Context of existing literature
    - Literature which conflicts with the findings of this study
    - Literature which is consistent with the findings of this study
- Exploration of results
    - Study limitations
    - Other explanations for study findings
- Future areas for research
- Conclusions
- Chapter 9 Summary

Summary of findings

The baseline results of this study demonstrated no difference in performance on neuropsychological tests between cases in NVAF and controls in sinus rhythm, with no effect of antithrombotic therapy. In addition, the follow-up results showed improvement in more sub-tests in controls than cases, but also more deterioration; the pattern of change seen when comparing cases and controls is not consistent with the expected effect of AF on cognitive decline, and these findings are not consistent with an overall deterioration in performance. Overall, the findings of this study provide no evidence to suggest an association between NVAF and performance on neuropsychological tests, nor change in performance over time.

Context of Existing literature

i) Literature which conflicts with the findings of this study

a) Studies of NVAF and cognitive impairment

Previous, predominantly cross-sectional studies have demonstrated an association between NVAF and poor performance on neuropsychological assessment. The findings of these studies are described in Chapter 2. The quality of previous studies is shown in table 9.1. The results of this study, both cross-sectional and longitudinal, conflict with these findings by failing to demonstrate a convincing difference at baseline or 12-month follow-up between patients with NVAF and controls. Furthermore, there was no demonstrable difference between patients on different forms of antithrombotic therapy. Possible reasons for these important findings, in the context of existing literature, include: -

Design: The most appropriate design for any study of cognitive function includes measurement of change in performance over time; [169] and the ideal study design for exploring this subject is an inception cohort study comparing cases in NVAF and matched controls in

sinus rhythm. Nearly all previous studies were cross-sectional in design. The only exception was a highly selective study comparing pre- and post-operative cognitive function after cardiac surgery in those who did and did not develop NVAF, with a follow-up period of just six weeks. [16] Participants have been shown to exhibit greater cognitive decline with age when analysed cross-sectionally and sequentially, than when the analysis of the cohort is undertaken using a longitudinal approach. [331] This suggests that these previous cross-sectional analyses may over-estimate the extent of cognitive decline. In addition, two of the previous studies did not aim to explore the association between NVAF and cognitive function from the outset, instead reporting the results of a sub-analysis of their cohort; [18,20]and only one study[17] included matched controls.

Sample: Most previous studies used small samples (44[20], 42[19], 16[17], 69[16] cases used compared with 174 in this study), although the Rotterdam study used 195 cases; [18] and two of the studies used highly selected inpatient populations. [16,19] The CAFE pilot study in Gateshead had a sample of 81 (27 cases). [15] Differences in patient characteristics include differing prevalence of diabetes (10% in CAFE versus 13.1%[20], 11%[18] and 27%[16] of the total sample of previous studies), and some age difference (although all participants were aged 55 or over). Five of the previous studies excluded those with previous stroke/ TIA, as did this study; although two did not (prevalence of 8.8%[20] and 3.2%[18] of total sample). In addition, many of these studies had more extensive exclusion criteria (and nevertheless found a positive association with cognitive decline), therefore the more limited exclusion criteria in the CAFÉ cohort are unlikely to have caused sufficient selection bias to affect the findings.

Representativeness: The CAFE cohort was maximally representative to ensure generalisability. Such generalisability was attained by recruiting participants in the community and minimising exclusion criteria, including co-morbidities where possible. In two previous studies,[16,19] sampling was of inpatients or secondary care registers, whilst one study[20] was of men only.

Potential confounders: Although others analysed the effect of potential confounders, the analysis of possible confounding effects in this study is far more comprehensive.

Duration of NVAF: The CAFE cohort was restricted to those with recent onset NVAF (<5 years), whilst others[17-20] did not report the duration of NVAF and may have included longstanding cases with potentially more progressive cognitive decline.

Neuropsychological tests: CAFE used a battery of tests measuring a wide range of cognitive domains (selective and divided/ sustained attention, verbal and non-verbal short and long-term memory, information processing and premorbid intelligence) in contrast to the limited neuropsychological assessment used by most previous studies. However, unlike CAFÉ, some previous cross-sectional studies have included measures of executive function including the Trail-Making Tests[16,20] and Wisconsin Sorting Card Test; [17] although two studies relied only on the MMSE for assessment of cognitive decline. [18,19] Therefore it is unlikely that the absence of a specific measure of executive function in our study is responsible for the difference between our results and those of previous studies.

Antithrombotic therapy: CAFE cases had higher levels of treatment with antithrombotic therapy (81.6%) than those of other older studies (26%[18], 50%[20], none[15], others not reported),

probably because treatment levels have increased since these studies, with greater awareness of appropriate management of NVAF. This treatment may reduce the risk of cognitive decline, although the subgroup analysis reported here provides no evidence for this.

b) Study of stroke risk and cognitive performance

A recent paper reporting further cross-sectional analysis of the Framingham Offspring Study cohort[43] demonstrated an inverse relationship between stroke risk and performance on neuropsychological tests measuring a range of cognitive domains (visual-spatial memory, attention, organisation, scanning and abstract reasoning). In particular, the presence of NVAF was found to be associated with poorer performance on tests of abstract reasoning and visual-spatial memory, although the study was not designed to look specifically at NVAF and the number of participants with NVAF was small (n= approximately 65). These findings support the suggestion that stroke risk is related to impairment of cognitive domains beyond executive function alone. Therefore it can be hypothesized that any cognitive impairment due to AF will also be present across multiple cognitive domains. Of the domains measured in the Framingham study, visual-spatial memory, attention and organisation are all measured as part of the CAFÉ neuropsychological test battery. For CAFÉ the measure of visual-spatial memory was a very similar test to that used by the Framingham study (visual reproduction of a figure with immediate and delayed recall), although the CAFÉ measures of attention were unrelated to the Framingham measures. However, since both studies (Framingham and CAFÉ) measured multiple domains, with some similarity in the domains measured, and because Framingham found changes in multiple domains, it is unlikely that the negative findings of the CAFE study are due to inadequate measurement of the executive function domain, as may have been suggested by previous literature.

ii) Literature which is consistent with the findings of this study

The only study on this subject to demonstrate lack of association between NVAF and cognitive impairment was the InCHIANTI study, which reported that after adjustment for age, atrial fibrillation was not significantly more prevalent in those with low cognitive performance with subcortical features than those with high cognitive performance or without subcortical features.[21] This study does support our findings, although it is smaller than CAFÉ and is focused on general cardiovascular risk factors rather than NVAF alone.

Table 9.1: Quality of studies of NVAF and cognitive decline

Quality criteria		Study						
		Kilander	**Sabatini**	**Farina**	**Rotterdam Study**	**Stanley**	**Geroldi**	**O'Connell**
Design		Cross-sectional sub-group analysis of longitudinal study	Cross-sectional study	Cross-sectional study	Cross-sectional analysis of a longitudinal study.	Longitudinal study comparing pre- and post-op cognitive function in cases who developed post-op AF	Cross-sectional analysis of a longitudinal study.	Case-control study
Controls		sinus rhythm, not matched	sinus rhythm, not matched	Paroxysmal AF, matched for age, education, hypertension	sinus rhythm, not matched	No post-op AF, not matched	sinus rhythm, not matched	sinus rhythm, age and sex matched
Study sample	**Cases (N)**	44	42	16	195	69	67	27
	Controls (N)	908	213	21	6389	239	417	54
	Well defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Representative?	Yes	No – inpatient	No- cardiology outpatients	Yes	No – highly selective	Yes – selected from population register	Yes – selected from community/ GP practices
	Selection bias	No	Yes: inpatient	Yes: outpatients	No	Yes – CABG patients	No – community based	No

Quality criteria		Study						
		Kilander	**Sabatini**	**Farina**	**Rotterdam Study**	**Stanley**	**Geroldi**	**O'Connell**
	Characteristics	Community-dwelling men aged 69-75 yrs.	Inpatients aged ≥70 years admitted to geriatric unit.	Cardiology outpatients attendees aged 49-72 years	Community dwelling aged ≥55 years, including institutions.	Patients undergoing CABG, 75% male, age range 56-76 years.	Community-dwelling men and women aged 70 to 84 years.	Community dwelling men and women, mean age 71.96 years
	Exclusion of those with prior stroke?	No – prevalence of 8.9%	Yes (prior stroke or TIA)	Yes (prior stroke or TIA)	No- prevalence of 3.2%	Yes – prior stroke with residual deficit	Yes (history of stroke)	Yes (prior stroke or TIA)
	Exclusion of those with dementia	No	Yes	Yes	No –study is looking at dementia prevalence	Yes	No	Yes
	Patients taking antithrombotic therapy (%)	50	Not reported	Aspirin= 43.8 Warfarin=31.3 Either=75.1	26	Not reported	Not reported	Yes – those on warfarin excluded
Analysis of potential confounders undertaken?		Age, education, LVEF, BP, DM, occupation, MI	APACHE II score, GDS, IASL	No- not reported	BP, DM, MI, education, medication, age	Baseline cognitive function, education, age, DM, LVEF, MI	Yes – cardiovascular risk factors, age.	Through analysis of extent of matching – groups equally matched for medical history except for CHF

Quality criteria		Study						
		Kilander	**Sabatini**	**Farina**	**Rotterdam Study**	**Stanley**	**Geroldi**	**O'Connell**
Outcome criteria	**Neuropscy. tests used**	1) MMSE 2) Trail Making Tests	MMSE	Digit Span, Digit Symbol, Logical Memory, Paired Associated Learning Test, Corsi's Block Tapping Test, Attentional Matrices, Raven Progressive Matrices, Judgement of Line Orientation, Rey Figure, Verbal Fluency for letters, Wisconsin Sorting Card Test	1) MMSE to define cognitive impairment) 2) more thorough assessment for dementia	1) Randt Memory, 2) Digit Span, 3) Digit Symbol, 4)Wechsler Memory Scale Figural Memory, 5) Trail Making, 6)Rey Auditory Verbal learning	MMSE	MMSE, NART, WMS logical memory, WMS digit span, PASAT, Tests of everyday attention (telephone task and map search)
	Blinding?	No - not reported	No- not reported	No-not reported	No-not reported	Yes	No – not reported	No – not reported

Exploration of findings:

The CAFE study found no apparent relationship between NVAF and change in performance on our neuropsychological tests over 12 months, with no effect of antithrombotic therapy. These findings could reflect a lack of association between cognitive decline and atrial fibrillation. Other explanations are discussed below: -

A) Study Limitations

1. Length of follow-up period

The follow-up period of 12 months may have been too short to observe a significant change in cognitive function. The study team has therefore obtained funding from the Stroke Association and have just started three-year follow-ups of the original CAFE cohort in order to determine whether cognitive function declines over a longer follow-up period.

2. Neuropsychological test battery

Important cognitive domains in vascular cognitive impairment:

Literature suggests that vascular cognitive impairment is related to executive function, speed, attention and information processing more than other domains.[317] However, one recent report from the Framingham study demonstrated an association between stroke risk (including NVAF) and lower cognitive performance across multiple cognitive domains, including visual-spatial memory.[43] In addition, previous cross-sectional studies (discussed above) demonstrated significant associations between NVAF and cognitive function despite several of these studies relying on MMSE alone, with no measure of executive function, speed or processing. Nevertheless, it is important to explore these domains further:-

- Executive function: Although the MMSE does contain a crude measure of executive function, and the Rey Figure has some executive components (problem solving, planning)

ideally the CAFE neuropsychological test battery would have included more extensive measures of executive function, and in a future study such measures would be added. Such measures may be more sensitive in detecting small changes in cognitive function due to NVAF. It is worth noting that although previous literature has suggested executive function is an important domain in vascular cognitive impairment, it does not suggest that this is the only domain that may be affected.

- Speed of processing: The CAFE neuropsychological test battery contained several valid measures of attention, speed and information processing. However, it would have been useful to have more measures of speed of processing (e.g. computerised tests), since changes in speed of processing is also reported to be a relatively early change in the natural history of vascular cognitive decline. However, several of the CAFE subtests had speed components, and these did not show significantly greater change over time than tests of other domains.

Practice effects:

Possible explanations for the widely varying direction of changes in score for controls (equal numbers of tests improve and deteriorate) may include learning effect for some tests, as well as increased confidence due to familiarity with the study and observer.[271] For example, practice effects of 10% improvement have been demonstrated for the Rey Figure when retested after 1 month for the same figure, therefore CAFE may have benefited from using the Taylor figure (a similar figure to the Rey) at follow-up.[216] A study of elderly patients found the copy was not reliable with retesting at one year, although the delayed recall was moderately reliable at this time interval.[216,278] Another example of the effect of practice is for the Logical Memory test: an average gain in score of 1 point after one year in a young group,[225,246] and 0.7 points in one year in an older group (mean 69 years) has been

demonstrated due to practice effects.[225,318] Therefore the CAFE follow-up findings may underestimate cognitive decline for this subtest.

Differential protective effect of good cognitive reserve:

Good cognitive reserve may mask early verbal memory dysfunction more than visuo-spatial dysfunction,[319] although this is not likely to affect the results of this study since there was no convincing change in either domain.

NART pronunciation:

It may have reduced bias to have used a tape-recorder to double-check NART pronunciations. In addition, it may have been helpful to have used the Cambridge Contextual Reading Test (CCRT) (see Chapter5), which has been shown to be more accurate than NART in measuring premorbid intelligence in those with mild dementia.

Combined scores:

In CAFÉ, as with most studies using Wechsler tests, the digits forwards and digits backwards scores were combined to obtain one score, with the assumption that the two tests behave similarly. However, it has been suggested that as age increases after 80 years, forward span remains stable but backwards deteriorates.[225,274] Therefore combining the scores may have hidden important differences. In future studies the scores might therefore be analysed separately.

Auditory tests and hearing problems:

It is possible that tests involving auditory material (Telephone Tasks, PASAT) may be affected by hearing problems and/ or interference on the cassette tapes. However, the

Telephone task had been validated using the most inexpensive tape recorder on the market, providing reassurance that high quality equipment was not required. In addition, participants in CAFE were asked if volume level was appropriate, and those with severe hearing problems were excluded from the study (test validation by the authors had included mild hearing impairment, which did not have an effect on the results[295]). Similarly, those with visual problems may have had difficulties with the Map Search test.[212] As suggested by the test authors,[295] CAFÉ participants who reported difficulty in seeing the symbols were excluded.

Informant information:

Further validation of the CAFÉ battery with an informant questionnaire, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[320] may have been helpful.

Subtests of larger batteries:

Because some of the CAFE sub-tests represent sub-tests of other, larger scales (e.g. Logical Memory and Digit from WMS), the literature on these individual sub-tests was limited, and tended to refer to the whole scale total scores (e.g. Wechsler's 'Memory Quotient') etc. rather than detailed information on the subtest used in CAFE. However, there are a number of other test batteries which use subtests in this way.[225]

Combining scores with demographic information:

CAFE, unlike some other studies, did not use demographic information (education, sex) in conjunction with NART errors to arrive at IQ.[216,218,239] Doing this may perhaps have given better estimates of premorbid cognitive functioning.

Bilateral infarcts and the WMS:

Logical Memory and digits forwards measure memory functions which are equally represented in both hemispheres, therefore damage to one side of the brain only (e.g. unilateral silent infarcts) may have no effect on the performance of this sub-test.[266] Therefore lack of deterioration in this subtest may not necessarily reflect absence of brain injury, rather is more likely to suggest absence of bilateral brain injury. This may have led to underestimation of the extent of silent infarcts in this study, although ultimately would not affect the primary outcome measure, that is the extent of change in the neuropsychological tests over the follow-up period.

Reliability of Telephone task:

Although reliability of telephone search while counting (dual task decrement) was satisfactory for two groups of non-brain-damaged subjects (0.51 and 0.61) it was lower in a group of participants with stroke (0.40).[228] This may lead to underestimation of cognitive decline in this study, since the hypothesized pathological mechanism for cognitive decline in our cohort is through silent infarcts.

Task motivation:

Neuropsychological tests are dependent upon patient motivation and compliance, therefore it would have been helpful to have had an explicit measure of task motivation in the test battery. However, for this study there was no financial or other incentive to perform badly, unlike studies of other groups where such incentives may exist (e.g. in cases of head injury). Measures of task motivation and test validity include clinical judgement, performance patterns present in existing neuropsychological testing and more formal measures.[261]

Variability in administration:

The two tests subject to the greatest variability in administration are the LMS (*unrevised WAIS) and Rey figure (criteria are few and therefore there is considerable variability between scorers.[225,261] However, CAFE used the revised version of the LMS, reported as more reliable, and incorporated objective interrater checks for scoring the Rey Figure.

3. Confounding factors

It has been suggested that detection of both participants in a preclinical stage of dementia and those with prevalent dementia could be missed because of insensitivity of neuropsychological tests to age, education and sex. To improve the accuracy of detecting dementia, it is recommended that test results need to be used in combination with analysis of potential confounders, particularly age, sex and education.[169] In the CAFÉ baseline analysis, these potential confounders were thoroughly analysed.

Whilst there were differences between cases and controls for diabetes, cholesterol, CHD, CHF and SF-36 score, these did not confound the findings based on the age-adjusted comparisons between cases and controls and between treatment subgroups.

Although mental health status was measured using the SF-36, a more specific measure of depression may be preferable when studying cognitive decline; therefore the Geriatric Depression Scale[321] has been incorporated into further follow-up visits of this cohort.

4. Attrition and 'healthy survivor' effects

The attrition rate between baseline and follow-up at 12 months was 16%. It is possible that the factor(s) influencing whether or not participants were included at follow-up also

influenced their cognitive performance; or that cognitive performance affected completion of 12-month follow-up assessments.

Although clearly there was no 12 month cognitive data for those who were lost to follow up, analysis comparing those who did and did not complete follow-up did not suggest marked differences that would be likely to affect the findings in this way. With hindsight, it may have been appropriate to model the expected cognitive decline of those lost to follow-up, by assuming normal distribution of baseline cognitive function and with use of the Markov chain Monte Carlo technique for modelling longitudinal studies.[198,322] In this way it would have been possible to estimate the change in cognitive function of the cohort taking into account those lost to follow-up. However, it was felt that the baseline cognitive function of this cohort was not sufficiently normal for appropriate use of this method. Instead, the results were presented with the effect of attrition made explicit.

In addition, although 16% appears to be a high attrition rate, when compared to other studies of elderly cohorts, which have attrition rates of up to 80%,[160] this attrition rate is not excessive. Nevertheless, it is possible that our findings may have been affected by the healthy survivor effect, since studies have shown that those with cognitive impairment and dementia have higher mortality than those without.[174,176,323,324] For this reason, attrition due to mortality in any study of cognitive function may lead to bias and underestimation of the extent of cognitive impairment in both cases and controls. However, this survival effect is likely to be stronger in more severe dementia, [18] and therefore should not greatly affect our cohort. Nonetheless it is possible that some healthy survivor effect may have contributed to our negative findings, but is unlikely to fully explain them.

5. Selection and response bias

Notes screening

Screening of 2866 sets of notes in general practice led to inclusion of only 362 participants in the study at baseline. This led to concern that selection bias may have taken place such that those who were included had specific characteristics, different to those who were not included, which may influence their performance on neuropsychological tests. However, analysis comparing those who did or did not respond to invitation to participate did not suggest significant differences that would be likely to affect the findings in this way.

Only limited information had been recorded for those who were screened but not selected for invitation to participate, therefore the possibility of selection bias could not be ruled out. However, the protocol for screening of notes was objective and systematic, and used only the study's inclusion criteria. In this way, there is no logical reason why selection bias would have occurred.

Nature of participation in the study:

Response bias is possible due the nature of participation in this study, through recruitment methods and protocol design:

- Patients were invited to participate by letter counter-signed by their GP, therefore the relationship of the potential participant with their GP and health services in general may have influenced their decision to participate.
- Invitation by letter would have prevented those who are unable to read from participating in the study, although these would have been excluded from the study in any case.
- Patients were visited at home in an attempt to avoid the inconvenience of travelling to a research centre, which may have dissuaded people from participating. Despite this however, it

is possible that the more frail potential participants would be less inclined to participate, and this was explored further in the analysis of potential confounders.

Characteristics of general practices:

The method of selection of general practices (choosing larger practices first) is unlikely to have led to response bias since ultimately the majority of practices in the study area were selected, representing a wide spectrum of characteristics including large and small practice list size, single-handed GPs and group practices.

Differences between the total study population characteristics and characteristics of the population from which the sample was drawn:

The characteristics of the total study population may bias the results if they differ from the general population from which the sample is drawn. This issue is explored further under 'inclusion and exclusion criteria' (below).

Differences between characteristics of responders and non-responders:

Possible sources of non-response bias are suggested by the significant differences in those who did and did not complete baseline interview in that: a) female non-responders (median age 79 years) were significantly (p=0.001) older than female responders (median age 77 years); and b) non-responders had significantly (p=0.009) less record of CHD (29% of non-responders vs. 37% of responders). Exploring these differences further:-

a) Since there was no significant difference in age for men in these two categories, and because the difference between the two groups for women was small (though statistically significant), it is unlikely that age difference would considerably bias the results.

b) However, it is possible that the greater morbidity from CHD in the responder group may affect the findings. A high prevalence of morbidity from CHD would be expected in our cohort because the inclusion criteria for cases necessitate a diagnosis of NVAF, which is often associated with CHD. Greater morbidity from CHD in the responder group is more surprising however. Reasons for this may include: that those with known cardiac problems might be more interested in participating in a study which is described to them as exploring links between the heart and memory; that those with CHD have more contact with the health services and therefore feel more comfortable with further involvement with health professionals or are inclined to 'give something back'; that those with CHD experience symptoms of cognitive decline and are interested in involvement in the study for that reason. This latter possible explanation would bias the study results, as would an association between CHD and cognitive decline even if patients were unaware of symptoms.

Ways to remove this potential source of bias include changes to recruitment methods. However, ischaemic heart disease is a major risk factor for NVAF, and in order to recruit a representative sample of older people with NVAF, it would have been inappropriate to exclude those with CHD. Therefore any potential confounding effect of CHD was thoroughly explored in the analysis of baseline cognitive function results.

6. Inclusion and exclusion criteria

The inclusion criteria for this study were selected to maximise generalisability of the results to the general population (by recruiting in the community and minimising exclusion criteria), whilst making it possible to address the specific research question. In establishing these criteria, it was inevitable that the results would need to be interpreted with explicit awareness of the limitations that any selection criteria impose. Particular criteria that undoubtedly have an influence on the study's findings are:-

1) Exclusion of those who have suffered any stroke or transient ischaemic attack.

This study was explicitly designed to exclude those with the major proven risk factors for cognitive decline and dementia, since their inclusion would make it very difficult to establish a causal link with NVAF rather than the proven risk factor. For this reason those with prior cerebrovascular events and severe heart failure were also excluded. In excluding those with stroke, selection bias or 'harvesting' may have been introduced, since this group of patients may indeed have been those at highest risk of cognitive impairment due to NVAF. The proposed causal mechanisms for cognitive decline in NVAF include silent cerebral infarction, therefore those who suffer stroke by the same pathological mechanism may have been at risk of considerable cognitive decline due to NVAF. This issue is highlighted by the Rotterdam Study, [18] which found that NVAF was associated most strongly with Alzheimer's Disease with cerebrovascular disease (OR= 4.1), and had a weaker association with vascular dementia (OR=1.9). Exclusion of those with stroke may therefore have significantly underestimated the risk of cognitive decline in this cohort. However, four of seven other published studies[15,16,17,19] that found a positive association between NVAF and cognitive decline also excluded those with stroke/ TIA and thus have the same potential for selection bias. In addition, although those with stroke may have had silent infarcts related to NVAF, with

resultant cognitive decline, the literature suggests that post-stroke dementia is due to a wide-range of pathologies including haemorrhage, multiple infarcts, single strategic infarcts and small vessel disease, thus inclusion of patients with a history of stroke would have made interpretation of cognitive impairment in this group difficult.[317,325] In addition, inclusion of this group would have been logistically difficult and other effects of stroke (perceptual, motor and sensory including visual problems) would have made completion of the neuropsychological tests impossible or misleading.

2) Exclusion of those with established dementia or MMSE<24.

The aim of our study was to explore the hypothesised relationship between NVAF and potentially preventable cognitive decline and thus patients already diagnosed as having dementia were excluded. However, this group may have had dementia due to NVAF, therefore their exclusion may have led to underestimation of the extent of cognitive decline in those with NVAF. Nevertheless, completion of the neuropsychological test by this group would have been extremely difficult and accurate comparison of baseline and follow-up results would not have been possible.

In summary, the design of our prospective cohort study made the use of certain exclusion criteria unavoidable, and may therefore have led to underestimation of the extent of cognitive decline in our population. However, it is unlikely that this alone is sufficient to explain our negative findings.

7. Imaging

Ideally, this study would have included magnetic resonance imaging (MRI) of the brains of all or some participants. This would have provided insight into possible pathological explanations for the findings. However lack of resources, despite many applications for funding, made this impossible.

Since the findings were negative, proof of the hypothesized pathological mechanism (i.e. silent cerebral infarction) by brain imaging would have been less helpful than had the findings been positive. In addition, one study of 80 year-olds demonstrated that, although related to intelligence, ischaemic effects (periventricular and deep white-matter hyperintensities) alone are only responsible for part of the great variation in cognitive decline between individuals.[326] Therefore the true measurement of change in cognitive function, as in this study, is more appropriate than imaging alone.

B) Other explanations for study findings

1. Speed of cognitive processing:

Literature suggests that neuropsychological test scores which have a speed component may change over a shorter follow-up period that those which measure other cognitive functions.[317] However, even when those tests of the CAFE battery which had a speed component were grouped together, there were no significant findings.

2. Paroxysmal NVAF:

ECG recording was not repeated at follow-up, therefore those with paroxysmal AF may have been included in CAFE. However, studies show that those with paroxysmal AF had similar rates of stroke and stroke risk factors to those with permanent AF,[327] with no significant effect of intermittency on risk of thromboembolism.[328] Therefore this would be unlikely to bias our findings.

3. Duration of NVAF:

The time since onset of NVAF reflects the time since onset of potential risk of cognitive decline, therefore this may bias the results. All of the participants in this study had known duration of NVAF of <5 years. However, data from the SPAF study confirms that the duration of NVAF is not significantly related to risk of thromboembolism,[328] therefore it is unlikely that this would have an effect on silent infarcts and vascular cognitive decline.

4. Other antithrombotic drugs:

This study did not analyse effect of other antiplatelet agents such as dipyridamole or clopidogrel, only the antithrombotic drugs aspirin and warfarin. However, one study of

dipyridamole demonstrated that it was no more effective at reducing the risk of stroke than aspirin alone.[329] In addition, the CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) study demonstrated that clopidogrel was only more effective than aspirin in preventing stroke in a subgroup of patients with peripheral arterial disease.[332] Therefore it is unlikely that this would have had a great effect on our findings, particularly when the use of this drug is still relatively low.

5. Problems with searching the literature:

There were few studies reporting a lack of association between a potential risk factor and cognitive decline (i.e. negative findings) – this may be due to publication bias, and re-emphasises the need to report negative findings such as those from this study.

6. Mortality and cognitive decline:

As discussed in Chapter 3, cognitive impairment and decline is associated with mortality therefore it is possible that our findings may have been affected by the healthy survivor effect. This could potentially have led to underestimation of the extent of cognitive impairment in both cases and controls. For this reason, attrition due to mortality in any study of cognitive decline will lead to bias. Fortunately, this study's rate of attrition due to mortality was relatively low (4.4%).

C) Summary of exploration of findings

Of the limitations discussed above, one of the most important is that after careful examination of the literature I now feel that the duration of follow-up may have been too short, such that a true association between NVAF and cognitive decline, though not apparent at 12 months, may

be demonstrated with longer follow-up. In addition, the majority of CAFÉ participants were on antithrombotic therapy and this may have protected them against cognitive decline (although this did not appear to be the case when the treatment subgroups were analysed). Nevertheless, despite these and other limitations, this work was carried out with rigour using a representative, reasonably large sample and longitudinal design; therefore in my opinion the findings that there is no association between NVAF and cognitive decline over (specifically) 12 months are valid. In addition, there is evidence to accept the null hypothesis that: 1) the cognitive function of people with NVAF is no different to that of age and sex-matched controls in sinus rhythm, when assessed by detailed neuropsychological testing; and 2) the decline in cognitive function over time (over 12 months) in people with NVAF is no different to that of controls. However, the findings of this study do not provide evidence to reject the hypothesis that decline in cognitive function over a longer period of time (i.e. more than 12 months) in people with NVAF is different to that of controls, nor that there is an association between untreated NVAF and cognitive decline.

Future areas for research

- The work reported in this thesis informs future research studies by demonstrating the usefulness of longitudinal studies of representative populations in exploring change in cognitive function, and the necessity of an adequate interval between baseline and follow-up. In addition, it highlights the importance of measuring multiple cognitive domains.
- More large, longitudinal cohort studies of atrial fibrillation and cognitive decline are needed to confirm or refute the negative findings from the study reported here. A further follow-up (at 3 years) of the CAFE cohort is underway.
- In particular, future studies should be of adequate duration, and should use an internationally recognised 'gold-standard' neuropsychological test battery that contains sensitive assessment

tools to detect small changes in cognitive function within the follow-up period. The development of such a test battery, which as yet is not available, should be a research priority.[160]

Conclusions

The results of this study fail to confirm the findings of previous research addressing the association between NVAF and cognitive decline, which to date has been predominantly restricted to small cross-sectional studies of selective populations with neither careful consideration of potential confounders nor of the effect of antithrombotic therapy.

The findings of the CAFE study accept the original null hypotheses that: 1) the cognitive function of people with NVAF is no different to that of age and sex-matched controls in sinus rhythm, when assessed by detailed neuropsychological testing; and 2) the decline in cognitive function over time (over 12 months) in people with NVAF is no different to that of controls. These results are likely to be more reliable and valid than those of the preceding studies since they derive from a larger, representative community-based population and represent longitudinal data. CAFE's results are also more likely to represent the real relationship between cognitive decline and NVAF in today's UK population since these findings incorporate current treatment levels with antithrombotic therapy. As such, they contrast with previous studies that were performed prior to initiatives such as the National Service Framework for Coronary Heart Disease[330], and may now be out of date.

In conclusion, this study finds no convincing difference in cognitive function nor cognitive decline over 12 months, between cases with recent onset NVAF and controls, nor between patients on anticoagulant/ antiplatelet therapy and those untreated.

Chapter 9 Summary

- The findings from this study conflict with previous studies in this field. However, previous studies were of lesser quality and less appropriate design. No previous high quality longitudinal studies of this research question have been published.
- As with all studies of this nature, there are a number of potential areas of bias and possibilities for underestimation of the true extent of cognitive decline in this cohort. Limitations to this study included short duration of follow-up, neuropsychological tests used and attrition of participants. These limitations need to be weighed against the advantages of generalisability of the results of this study to the general population, and the logistics of undertaking a substantial piece of research in the community. Despite these inevitable problems, a very extensive analysis of our results persistently demonstrated no clinically important differences between those with and without NVAF, nor between those with and without treatment with antithrombotic therapy. Therefore, in spite of the limitations described, in my opinion the findings that there is no association between NVAF and cognitive decline over (specifically) 12 months are valid. In addition, there is evidence to accept the null hypotheses that 1) the cognitive function of people with NVAF is no different to that of age and sex-matched controls in sinus rhythm, when assessed by detailed neuropsychological testing; and 2) the decline in cognitive function over time (over 12 months) in people with NVAF is no different to that of controls. However, the findings of this study do not provide evidence to reject the hypothesis that decline in cognitive function over a longer period of time (i.e. more than 12 months) in people with NVAF is different to that of controls, nor that there is an association between untreated NVAF and cognitive decline.
- Further research suggested by our findings includes more longitudinal studies of cognitive decline in NVAF, and include completion of the three-year follow-up of this study cohort.

Summary of thesis

This chapter represents a collation of the summaries of all previous chapters in this thesis.

Background

- To inform the work reported in this thesis, an extensive review of relevant literature was undertaken, with separate searches addressing; 1) studies of atrial fibrillation (AF), silent cerebral infarction and cognitive decline; 2) studies of the epidemiology of AF and 3) studies of other risk factors for cognitive decline.
- There is evidence for associations between AF, silent cerebral infarction and cognition, but to data this has been largely from cross-sectional studies, including the pilot study carried out prior to the work reported in this thesis. In order to adequately explore the aetiology of cognitive decline, longitudinal studies of representative populations, measuring cognitive function over an appropriate period of time are needed. The work reported in this thesis is such a study.
- AF is a common condition, the prevalence of which increases as the population ages. Studies of people with AF report previous stroke/ TIA, age>75 years, history of hypertension, left ventricular dysfunction and diabetes as risk factors for stroke in AF. It is plausible that these may also be risk factors for silent stroke leading to cognitive decline in those with AF.
- Despite the proven efficacy of anticoagulant and antiplatelet therapy in preventing stroke in people with AF, there is significant underprescribing of these treatments. The work reported in this thesis addresses the role of anticoagulant and antiplatelet therapy in preventing cognitive decline in addition to stroke.
- There are many studies of risk factors for cognitive decline other than AF. The most widely studied risk factor is hypertension, for which evidence suggests there may be a modest association with cognitive decline. There is also strong evidence supporting the association between age and cognitive decline.

- A comprehensive review of the literature on the epidemiology of cognitive decline consisted of a formal systematic review of cognitive decline in the general elderly population. In addition specific searches for literature covering issues of relevance to the work reported in this thesis were undertaken where appropriate.
- A number of issues in cognitive function research methodology were identified, including the challenge of high attrition rates in elderly populations, the need for longitudinal studies when looking at change over time and the effect of cognitive function on mortality leading to survivor bias.
- Key findings from the systematic review were that cognitive decline is almost universal, that quality of studies in this area varies widely, that studies in this area are vulnerable to bias, particularly selection and survivor bias, and that there is a need for a gold-standard battery of neuropsychological tests in order to make studies of cognitive decline comparable.
- The CAFE study neuropsychological test battery was selected because it had developed for the purpose of examining cognitive impairment due to cerebrovascular disease, had been used in the CAFE pilot study, had been validated, was portable and measured a range of cognitive domains (general cognitive function, pre-morbid intelligence, verbal long term memory, short term memory, information processing and attention, selective attention, divided attention and non-verbal memory).
- The tests in the CAFE battery were the Rey Complex Figure, the Mini Mental State Examination, the Logical Memory and Digit Span subtests of the Wechsler Memory Scale (WMS), the Map Search and Telephone Task subtests of Tests of Everyday Attention, and the Paced Auditory Serial Addition Test. In addition the National Adult Reading Test (NART) was used to measure premorbid intelligence.
- A literature search was undertaken to examine the clinical significance, reliability, sensitivity and validity of performance on the subtests of the CAFE battery. Overall, there was reasonable

evidence of reliability and validity of the subtests for use on a cross-sectional basis. However, the literature search revealed very few reports on reliability, sensitivity or validity of the subtests in measuring change over time. In addition, the literature on clinical significance or clinical importance of performance on the subtests was extremely limited.

- Reports on the sensitivity of the tests in detecting dementia were far more plentiful than reports specifically addressing mild cognitive impairment or decline.

- CAFE baseline data compared well with normative data available on Logical Memory, Digit Span, MMSE and Rey Complex figure. However, for the NART and the Tests of Everyday Attention the CAFE cohort scored worse than the normative population. There was little correlation between NART IQ and performance on other tests in the CAFÉ battery at baseline; therefore it was unlikely that verbal intelligence would confound the findings.

- Overall, the CAFE neuropsychological test battery provides an acceptable method of measuring cognitive function in the cohort. Although evidence for reliability and validity of these tests in measuring change over time is limited, this appears to be the case for the majority of neuropsychological tests. Therefore choice of the tests was made on other grounds, namely the range of cognitive domains tested, and practical factors such as ease of administration, portability and time constraints.

Methods

- Participants were recruited via general practices. Electronic and paper GP notes were screened using inclusions and exclusion criteria and potential participants were invited by letter to take part in the study.
- Baseline interview consisted of a validated neuropsychological assessment, health questionnaire, assessment of health status, physical examination, limb-lead ECG and blood tests. Follow-up examination at 12 months consisted of the same neuropsychological assessment, health questionnaire and assessment of health status.
- Validation of all components of both interviews was undertaken where possible.
- Ethical approval was obtained for this study from the Sunderland Local Research Ethics Committee and the South Tyneside Local Research Ethics Committee.

Results- baseline

- Participants were recruited from general practices from in Sunderland and South Tyneside, which ranged from large practices with list sizes of 14,500 patients to small, single-handed practices.
- 43% of notes screened were included as potential participants, with the major reasons for exclusion at this stage being history of stroke/TIA or person not in chronic NVAF.
- Stages of recruitment involved applying exclusion criteria during screening of notes in general practice and at baseline interview. A large proportion (55%) of potential participants declined to take part after invitation, and a smaller proportion (14%) were excluded at interview.
- Female responders were slightly younger than female non-responders (median 77 versus 79 years) and responders were more likely to have a record of CHD and to have taken aspirin than non-responders. There were no significant differences between responders

and non-responders for other characteristics or documented co-morbidities (atrial fibrillation, CHF, hypertension, diabetes, thyrotoxicosis, Parkinson's, peripheral vascular disease and depression).

- The median age of the CAFE cohort was 75 years; 56% were male, 37% had a record of CHD, 6.6% had CHF; 38.4% had a record of hypertension and 10.2% had a record of diabetes.
- Characteristics of the cohort were examined with comparison of cases and controls. There were significant differences between cases and controls for measures of diabetes, cholesterol level, CHD, CHF and SF-36 score. These key variables were noted for incorporation into subsequent analysis of potential confounders.

Results- follow-up

- The only significant differences between those who did and did not complete the follow-up interview were that those who completed the follow-up had better baseline scores for the physical activity and general health domains of the SF-36.
- When the total study population was analysed without stratification, change in performance on the neuropsychological tests between baseline and follow-up was not significant for most tests.
- When cases and controls were analysed separately, the overall direction of change in test scores over the follow-up period varied widely, in that for both groups, there was an overall improvement in some sub-tests and deterioration in others. However, the change in test score was only statistically significant ($p<0.05$) for a proportion of the tests: cases demonstrated overall improvement in two subtests and deterioration in four subtests; controls showed improvement and deterioration in the same sub-tests as for cases, but also showed improvement in a further six subtests and deterioration in a further four subtests. These findings are not consistent with an overall deterioration in performance on neuropsychological

testing in atrial fibrillation compared to sinus rhythm, and thus support the null hypothesis that there is no consistent association between NVAF and cognitive decline over 12 months.

- The overall direction of change (improvement or deterioration) varied between subtests which assessed the same cognitive domain, and there were no statistically significant differences between the proportion of cases and controls that improved, deteriorated or stayed the same for each subtest over the 12-month follow-up period.
- There were no statistically significant differences in most neuropsychological test scores, between cases and controls on aspirin, warfarin or neither therapy.
- For nearly all subtests in the CAFE neuropsychological test battery, there was a highly significant correlation ($p<0.01$) between test score at baseline and test score at 12 month follow-up, suggesting very similar scores at baseline and score at follow-up for both cases and controls (for the majority of neuropsychological tests in the CAFÉ battery).
- Age and education did not confound the results when put into a regression model. In addition, Pearson's correlation techniques showed little relationship between age at baseline interview of the total population and change in the majority of neuropsychological test scores over the follow-up period.
- The number of participants who changed treatment subgroup according to antithrombotic therapy was small and did not impact upon the findings of the study.
- There did not appear to be a consistent relationship between stroke risk (using SPAF criteria) and change in performance on neuropsychological tests over follow-up.
- Overall, these results demonstrate no consistent or significant change in cognitive performance over the 12-month period for the total study population, and no consistent or significant difference in change in cognitive performance between cases and controls, nor between treatment subgroups. These findings support the null hypothesis that decline in cognitive function over time (12 months) in people with NVAF is no different to that of controls.

Discussion

- The findings from this study conflict with previous studies in this field. However, previous studies were of lesser quality and less appropriate (cross-sectional) design. No previous high quality longitudinal studies of this research question have been published to date.
- As with all studies of this nature, there are a number of potential areas of bias and possibilities for underestimation of the true extent of cognitive decline in this cohort, and limitations to this study included duration of follow-up, neuropsychological tests used and attrition of participants. These limitations need to be weighed against the advantages of generalisability of the results of this study in the general population, and the logistics of undertaking a substantial piece of research in the community. Despite these inevitable problems, a very extensive analysis of our results persistently demonstrated no clinically important differences between those with and without NVAF, nor between those with and without treatment with antithrombotic therapy. Therefore, in spite of the limitations described, in my opinion the findings that there is no association between NVAF and cognitive decline over (specifically) 12 months are valid. In addition, there is evidence to accept the null hypotheses that: 1) the cognitive function of people with NVAF is no different to that of age and sex-matched controls in sinus rhythm, when assessed by detailed neuropsychological testing; and 2) the decline in cognitive function over time (over 12 months) in people with NVAF is no different to that of controls. However, the findings of this study do not provide evidence to reject the hypothesis the decline in cognitive function over a longer period of time (i.e. more than 12 months) in people with NVAF is different to that of controls, nor that there is an association between untreated NVAF and cognitive decline.
- Further research suggested by our findings includes more longitudinal studies of cognitive decline in NVAF, and include completion of the three-year follow-up of this study.

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Appendices

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Appendix 1: Search strategies for literature searches.

i) AF as a risk factor for cognitive decline/ dementia (search 1)

Combination of the four strategies for aetiological and prognostic studies of AF and cognitive decline/ dementia last carried out on March 2nd 2004.

1, incidence.tw.,
2, exp mortality/
3, follow-up-studies.hw.
4, mo.fs.
5, prognos$.tw.
6, predict$.tw.
7, course.tw.
8, 1 or 2 or 3 or 4 or 5 or 6 or 7
9, (odds and ratio$).tw.
10, (relative and risk).tw.
11, (case and control$).tw.
12, exp cohort-studies/
13, exp risk/
14, 9 or 10 or 11 or 12 or 13
15, supraventric$.tw.
16, atria$.tw.
17, flutter.tw.
18, fibrill$.tw.
19, arrhythmi$.tw.
20, dysrhythmi$.tw.
21, tachy$.tw.
22, sick sinus.tw.
23, atrial fibrillation.sh.
24, atrial flutter.sh.
25, exp TACHYCARDIA, SUPRAVENTRICULAR/
26, sick sinus syndrome.sh.
27, ((15 or 16) and (17 or 18 or 19 or 20 or 21)) or 22
28, 23 or 24 or 25 or 26
29, 27 or 28
30, "Alzheimer-Disease"/
31, exp "Dementia-Vascular"/
32, "Lewy-Body-Disease"/
33, "Pick-Disease-of-the-Brain"/
34, "Kluver-Bucy-Syndrome"/
35, 30 and 31 and 32 and 33 and 34
36, 30 or 31 or 32 or 33 or 34
37, dement$.mp. [mp=title, abstract, name of substance, mesh subject heading]
38, alzheimer$.mp. [mp=title, abstract, name of substance, mesh subject heading]
39, (lewy$ and bod$).mp. [mp=title, abstract, name of substance, mesh subject heading]
40, ((cognit$ or memory$ or mental$) and (declin$ or impair$ or los$ or deteriorat$)).mp. [mp=title, abstract, name of substance, mesh subject heading]

41, (chronic and cerbrovascular).mp. [mp=title, abstract, name of substance, mesh subject heading]
42, ("organic brain syndrome" or "organic brain disease").mp. [mp=title, abstract, name of substance, mesh subject heading]
43, "benign senescent forgetfulness".mp. [mp=title, abstract, name of substance, mesh subject heading]
44, (cerebr$ and deteriorat$).mp. [mp=title, abstract, name of substance, mesh subject heading]
45, (cerebr$ and insufficien$).mp. [mp=title, abstract, name of substance, mesh subject heading]
46, (Pick$ and disease).ab,sh,ti.
47, Binswanger.ab,sh,ti.
48, Korsakoff$.ab,sh,ti.
49, "Korsakoff$-Syndrome"/
50, 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51, 36 or 50
52, 8 or 14
53, 29 and 51
54, 52 and 53

ii) Prognosis and natural history (used for searches 1 and 2)

From Oxford Centre for Evidence Based Medicine

1. incidence.tw.
2. exp mortality/
3. follow-up-studies.hw.
4. mo.fs.
5. prognos$.tw.
6. predict$.tw.
7. course.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

iii) Aetiology, causation and harm (used for searches 1 and 2)

From Oxford Centre for Evidence Based Medicine

1. (odds and ratio$).tw.
2. (relative and risk).tw.
3. (case and control$).tw.
4. exp cohort-studies/
5. exp risk/
6. 1 or 2 or 3 or 4 or 5

iv) Atrial fibrillation (used for searches 1 and 2)

Strategy for atrial fibrillation (Mark Sudlow MD thesis)

1. supraventric$.tw.
2. atria$.tw.
3. flutter.tw.
4. fibrill$.tw.
5. arrhythmi$.tw.
6. dysrhythmi$.tw.
7. tachy$.tw.
8. sick sinus.tw.
9. atrial fibrillation.sh.
10. atrial flutter.sh.
11. exp TACHYCARDIA, SUPRAVENTRICULAR/
12. sick sinus syndrome.sh.
13. ((1 or 2) and (3 or 4 or 5 or 6 or 7)) or 8
14. 9 or 10 or 11 or 12
15. 13 or 14

v) Stroke risk in atrial fibrillation (used as part of search 2)

Combination of AF strategy above and McMaster's aetiology strategy

1. case-control-studies.hw.
2. cohort-studies.hw.
3. 1 or 2
4. prognosis.tw.
5. survival-analysis.hw.
6. 4 or 5
7. 3 or 6
8. supraventric$.tw.
9. atria$.tw.
10. flutter.tw.
11. fibrill$.tw.
12. arrhythmi$.tw.
13. dysrhythmi$.tw.
14. tachy$.tw.
15. sick sinus.tw.
16. atrial fibrillation.sh.
17. atrial flutter.sh.
18. exp TACHYCARDIA, SUPRAVENTRICULAR/
19. sick sinus syndrome.sh.
20. ((8 or 9) and (10 or 11 or 12 or 13 or 14)) or 15
21. 16 or 17 or 18 or 19
22. 20 or 21
23. 7 and 22
24. *Cerebrovascular Accident/
25. 23 and 24

vi) Risk factors for cognitive decline (search 3 and Chapter 3 search –different inclusion criteria used)

This search combined a strategy for cognitive decline and dementia with a maximally specific aetiology strategy from Oxford Centre for Evidence Based Medicine, designed to retrieve articles on general risks for cognitive decline, not specifically AF. Search last performed on 2nd March 2004.

1. "Alzheimer-Disease"/
2. exp "Dementia-Vascular"/
3. "Lewy-Body-Disease"/
4. "Pick-Disease-of-the-Brain"/
5. "Kluver-Bucy-Syndrome"/
6. 1 and 2 and 3 and 4 and 5
7. 1 or 2 or 3 or 4 or 5
8. dement$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
9. alzheimer$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
10. (lewy$ and bod$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
11. ((cognit$ or memory$ or mental$) and (declin$ or impair$ or los$ or deteriorat$)).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
12. (chronic and cerbrovascular).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
13. ("organic brain syndrome" or "organic brain disease").mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
14. "benign senescent forgetfulness".mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
15. (cerebr$ and deteriorat$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
16. (cerebr$ and insufficien$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
17. (Pick$ and disease).ab,sh,ti.
18. Binswanger.ab,sh,ti.
19. Korsakoff$.ab,sh,ti.
20. "Korsakoff$-Syndrome"/
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 or 21
23. case-control-studies.hw.
24. cohort-studies.hw.
25. 23 or 24
26. 22 and 25

vii) Neuropsychological tests

This search was to determine clinical significance of and reliability in measuring change of the subtests in the CAFE test battery(on e-alert therefore last searched immediately prior to submission of thesis).

1. exp Reproducibility of Results/
2. exp *Neuropsychological Tests/cl, mt, st, sn [Classification, Methods, Standards, Statistics & Numerical Data]
3. exp *Wechsler Scales/sn, st [Statistics & Numerical Data, Standards]
4. *Attention/ or Tests of everyday attention.mp.
5. Rey figure.mp.
6. Tests of everyday attention.mp.
7. National Adult Reading Test.mp.
8. MMSE.mp.
9. Mini Mental State Examination.mp.
10. 8 and 9
11. 8 or 9
12. Paced Auditory Serial Addition Test.mp.
13. Clincal significance.mp.
14. clinical relevance.mp.
15. measurement of change.mp.
16. 1 or 14 or 15
17. 2 and 3 and 5 and 6 and 7 and 11 and 12
18. 2 or 3 or 5 or 6 or 7 or 11 or 12
19. 16 and 18
20. limit 19 to (human and english language and abstracts)

viii) Post-stroke dementia

1. Cognition Disorders/
2. limit 1 to ovid full text available
3. DEMENTIA/
4. limit 3 to ovid full text available
5. Cerebrovascular Accident/
6. 2 or 4
7. 5 and 6

Appendix 2: Forms used for Chapter 3 literature search

i) Box 1: In/out form

Study ID_____Endnote reference number_____

First Author_____Year_____Reviewer_____

	Participants	*Yes/No*
1 **2** **3**	Human, predominantly aged 60 years and over. Representative community sample. Not subgroups of the population which have been selected on the basis of existing specific illness.	
A	1 and 2 and 3 present?	

	Outcome	*Yes/No*
4 **5**	Rate of cognitive decline Nature of cognitive decline	
B	4 or 5 present?	

	Study designs and methodological quality	*Yes/No*
6 **7** **8**	Cohort study Prospective, with follow-up Community-based	
C	6, 7 and 8 present?	

Tick here if further discussion with second observer needed prior to final decision.	

'YES' to all of A, B and C = IN	
'NO' to any of A, B or C = OUT	

ii) Box 2: Data extraction sheet

*Instruction: complete the following sheet for all included papers. Note: it may not be possible to answer all questions for all papers. Answers to questions marked with an * will be transposed onto the summary spreadsheet.*

General Information: -

Reviewer: Date of extraction: Study ID*:

First author of paper: Year of Publication:

Eligibility Check:

Participants are human, representative community sample, not a group which have been pre-selected on the basis of existing specific illness and over 60 years?

Yes/No

Outcome measures are the rate (+/- nature) of cognitive decline? Yes / No

Study design is a prospective cohort study? Yes / No

If yes to all, continue:

Participants and setting:

Target population of the study:

Research question of the study?

*State outcomes (if any) other than cognitive decline which are used in the study:

Are all participants in the study suitable for inclusion, or is only a specific group within the main study suitable (e.g. controls)?

*Inclusion criteria (should be all-inclusive, but may need to re-evaluate based on studies obtained):

*Exclusion criteria (should be minimal, but may need to re-evaluate based on studies obtained):

*Recruitment procedure (relevant to response bias etc):

*Characteristics of the participants included at baseline:
Age range =
Ethnicity =
Sex =
(i) Other special characteristics of relevance =

Methods

Study design (should be prospective cohort study):
*Sample size required/ attained:

*Follow-up:
Total length of follow-up from baseline to final assessment =
Mean follow-up time=
Number of follow-up assessments =

***Neuropsychological test battery:**
How was cognition measured (give full details e.g. name of battery, where developed. whether widely used, tests included, which aspects of cognition are recorded etc)?

Were measurements at baseline and follow-up identical? (If not, how did they differ?)

*State other measures carried out at baseline:

*State other measures carried out at follow-up:

Analysis and Results

*What was the attrition rate?

*What was the level of non-participation?

*What % were followed up?

*What were the baseline cognitive function score(s)?

*What were the follow-up cognitive function score(s)?

*What was the rate of decline in cognitive function score(s)?

State any sub-group differences in the rate of cognitive decline:

*State any findings on the nature of cognitive decline - which aspects of cognition affected most (e.g. memory, attention, concentration), sub-group differences if any:

Miscellaneous:
Are these results duplicated in another paper in this review (if so, state study ID number)?

*Other notes and calculations:

iii) Box 3: Appraisal checklist and quality assessment form

(This information will be useful if an assessment of quality is required. An overall score is not appropriate.)

	Poor/ Not Reported	Fair	Good
Participants and setting:			
Is sample representative of the normal population?	X	X	X
Is the sample of patients well defined at the level of both invitation to participate and agreement to participate?	X	X	X
Methods			
Power calculation performed?	X	X	X
Objective and unbiased outcome criteria used:			
Clear, logical definitions for outcomes shown before the study started?	X	X	X
Had the neuropsychological test battery been validated? Are they sensitive to change and reliable for the purposes?	X	X	X
Did an appropriate professional carry out the neuropsychological testing? Was training provided if necessary?	X	X	X
Was the follow-up:			
Sufficiently long (long enough for outcomes to occur)?	X	X	X
Sufficiently complete (proportion of cohort followed up)?	X	X	X
Analysis and Results			
Were statistical techniques used appropriate? *(need to be suitable for analysis of change)*	X	X	X
Was there adjustment for important prognostic factors/ confounders?	X	X	X
Was there adequate f/u such that the level of non-participation does not influence the findings (thus reducing non-response bias?)	X	X	X
Was the attrition rate dealt with adequately?	X	X	X
Does the analysis account for the passage of time?	X	X	X
Was the study designed/ conducted so that other, unaccounted-for factors were unlikely to influence the outcome?	X	X	X
Are the estimates for risk of cognitive decline sufficiently precise (confidence intervals given?)	X	X	X

Other notes on quality:

Appendix 3: Neuropsychological tests

i) Outline of the neuropsychological test battery:

The following is a brief outline of how the tests are carried out. This does not contain the level of detail required to carry out the tests (such as is provided in test manuals), and is included here only to provide the reader with a basic idea of what the tests consist of and the logistics of the patient visits.

MMSE

This pen and paper test consists of asking the participant to answer questions/ perform short tasks in order to gain a measure of general cognitive function.

Logical Memory and Digit Span subtests of the Wechsler Memory Scale

Logical memory involves reading a tape recording of a short story to the participant, who is then immediately asked to recall information about the story. They are then asked to recall any information after a delay of 30 minutes from the original playing of the tape and again asked to recall information about the story. The participant is scored according to the amount of information they remember, and both raw scores and percentile scores can be obtained. The test is repeated with a different story. Note: for the CAFÉ study, the more recent 25 points for each story version was used.

Digit span involves reading out ever increasing strings of numbers, with the participant repeating each string immediately after the observer. The participant is scored according to the number of correct strings recalled. The process is then repeated with the participant asked to recall the string in reverse. Again, number of correct strings are recorded.

Rey Complex Figure

The participant is asked to copy a complicated figure and then to recall the figure (asked to draw it again) after 30 minutes. The figure is scored using a scoring sheet according to the accuracy and position of the components of the drawing.

Map Search and Telephone Task subtests of Tests of Everyday Attention

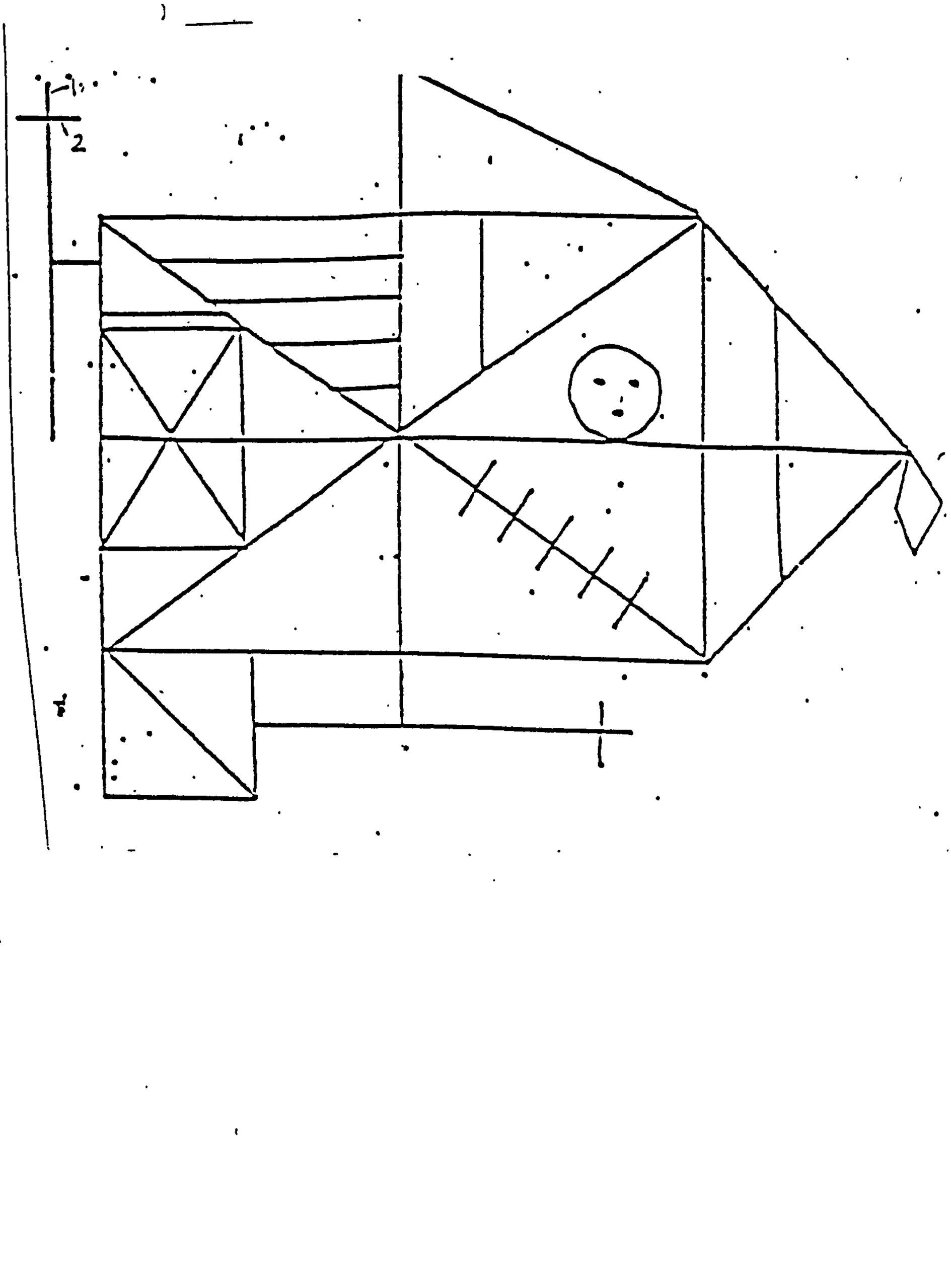
For the Map Search Task, the participant is provided with a map, on which there a number of symbols. The participant is asked to circle as many symbols as possible with a red pen for one minute, and then with a blue pen for one further minute. The number of symbols circled in the 1st and 2nd minute is recorded.

The Telephone Task consists of the participant being provided with a telephone directory, with two symbols shown after each telephone number. The participant is asked to circle any pairs of symbols, and the time taken is recorded. The task is repeated with a different telephone directory and the patient is then distracted by being asked to count beeps played on a tape recorder whilst circling the symbols.

Paced Auditory Serial Addition Test

This test consists of a tape recording of a list of numbers being played. The participant is asked to add consecutive numbers together and call out the answer. This test is repeated at two different speeds.

i) Rey figure



TEXT BOUND INTO THE SPINE

ii) **Map Search Task** (patient identifies symbols on the map below)


PHILADELPHIA
Camden
Trenton
Wilmington
Chester
Norristown
Willing-boro
Levittown
Burlington
Mount Holly
Medford
Lakes
Cherry Hill
Pennsauken
Marlton
Berlin
Gloucester City
Glassboro
Woodbury
Deptford
Haddonfield
Collingswood
Audubon
Westmont
Haddonfield
Magnolia
Somerdale
Stratford
Pine Hill
Runnemede
Glendora
Blackwood
Oak Valley
Mantua
Sewell
Barnsboro
Pitman
Hurffville
Turnersville
Whitman Square
Cross Keys
Williamstown
Monroeville
Clayton
Franklinville
Malaga
Elmer
Vineland
Millville
Bridgeton
Salem
Penns Grove
Carneys Point
Pennsville
Swedesboro
Woodstown
Pedricktown
Auburn
Oldmans Creek
Repaupo
Paulsboro
Gibbstown
Logan
Bridgeport
Swedesboro
Old Swedes Church
Mullica Hill
Harrisonville
Sharptown
Alloway
Quinton
Salem
Hancocks Bridge
Penns Grove
Carneys Point
Pennsville

HOUR SERVICE.....○❑ 831-8528
lumbing, Heating & Drains
Plumbing.....❑❑ 215-9475
mergency Service
A Magic Plumbing.....○○ 218-5862
OK Plumbing.....×○ 652-6940
xcellence in Service
bey Plumbing Associates.×❑ 211-9425
The Professionals"
le Plumbing Company.....❑× 764-7251
rompt & Efficient
e Plumbing.....×○ 206-3217
epairs Guaranteed
t Plumbers.....○❑ 263-2117
Complete Service
an Simpson, Plumber.....×○ 802-1841
lenghany Plumbing.....×× 953-6020
Established 1952
LLIED Plumbing Service....×❑ 275-8203
Your plumbing ally'
pha Plus Plumbers.....❑☆ 697-1508
The Quality Answer
mes Quall-Service.....☆❑ 409-6293
NDERSON BROS......○☆ 216-7373
Supply, Fit, Plumbing Supplies
pex Plumbers.....○☆ 218-5078
"Our Region's No. 1"
pex Plumbers.....×○ 780-8977
QUA-Way Plumbing.....❑× 803-9070
Honest advice; rapid action
rrow Plumbers.....☆○ 477-1408
"Will Visit Within 2 hrs After Your Call"
rrowhead Plumbing.....×❑ 215-4932
"A Name You Can Trust"
rt's Plumbing.....☆○ 258-8096
SPEN Plumbers.....☆☆ 348-5278
Plumbing Worries? Call us!
utoflow Plumbing.....○☆ 225-4220
We Install and Service all Brands
Baker, Marvin, Plumber.....○☆ 512-3476
Bedford Plumbing.....○× 290-7785
1-Year Guarantee of all Work
Bellweather Plumbers.....×❑ 226-6221
What we Fix, Stays Fixed!
ennett, Jacob, Plumber.....❑☆ 843-7906
enson Brothers.....☆○ 284-4132
We stand Behind Our Work
enson Plumbing & Heating.☆○ 215-2492
enton, G. & Sons.....○○ 473-2167
Fast, Efficient, Fair Prices
estway Plumbing.....×❑ 983-3411
Experienced, Lo Rates
loom's, Plumbing Service....×❑ 521-5824
"For Trouble-free Plumbing"
riar Plumbing Company.....❑☆ 218-4719
RYSTAN, GROUP, the .....☆❑ 213-3627
Brystan Plumbers
uilder's Emporium.....○☆ 553-7696
'We Know Our Job'
& B Plumbing.....☆☆ 954-5000
Quality Work Reasonably
. G. K......☆○ 223-2906
All Plumbing Services

Capitol City Plumbing.....○☆ 779-6267
Guaranteed to Please
Carr & Sons.....☆○ 585-4126
Drip/Leak Busters
Appliance Installation
CHAMPION Plumbers.....○☆ 218-0239
'The people you can trust'
Corey & Sons, Plumbers.....❑× 895-6381
"We want to Help"
Coulson Builders.....×❑ 379-7833
Plumbing our Speciality
Crenshaw Plumbing.....×☆ 963-3806
One in Your Area
Cummins, A., Plumber.....☆○ 256-8058
DP Plumbing.....○☆ 284-7639
Drains Unblocked
DVN Plumbing.....×❑ 214-4702
Dave's Plumbing & Heating...×× 215-7041
DAVIS, Joseph & Daughter..○× 843-7906
"The luckiest call you'll make today!"
Dawsons of Applegate.....❑○ 212-0437
Plumbing, Plumbing Supplies
Decor-Rite Plumbing.....☆❑ 315-8058
DRAINWELL Plumbers.....❑× 218-2157
The Best at an Affordable Price
Dyno-Rod.....☆☆ 215-1805
Repairs & Installation
EAMES Plumbers.....☆❑ 336-4126
Licensed Contractors
ELLIOTT, Mark.....○☆ 275-1305
No. 1 in Plumbing
Finbow, George & John.....×○ 216-6853
Serving 3 Counties area for over 20 years
Finchley, Amos, Plumber.....×○ 213-9523
FlowTech.....❑○ 235-2956
"Plumbing at its Best"
Forest Plumbers.....❑❑ 219-9215
"Solid Work, Fair Price"
Franklin Plumbing.....☆○ 702-3438
Radio-Controlled Cars
Friendly Plumbing.....☆× 860-1749
Domestic & Industrial
Garners, a Family Business...×☆ 257-6565
Plumbing, Heating, all Repairs
George Brown Plumbers.....○❑ 953-8813
Stockist, Ideal Standard
George Brown & Ptnrs......○❑ 662-2412
Plumbing
Latest Technology at Affordable Rates
Glen Plumbing Systems.....○○ 670-9221
We Back Our Work
Greens of Gateway.....×○ 570-1148
Plumbing/Heating
Grey & Company, Plumbers..×❑ 439-2156
'The small firm with the big reputation'
Guardian Plumber.....×○ 284-7541
'No Job Too Small'
Hancock Plumbing.....❑○ 921-8274
Free Quotations
Home Care Plumbing.....❑× 215-7411
(Four Offices)

Home Comfort.....❑× 452-8210
Licensed Plumbers
Home Depot Plumbers.....×× 362-6987
Low, Low Prices
Hudson Plumbing Contract ○❑ 216-8468
Free Consultations
Inter-City Plumbing.....❑☆ 245-8977
"A Name to Trust"
Jesse Jones Plumbing.....☆☆ 282-9023
Hassle-Free Service
John Peterson, Plumbing Contractor.....○× 657-9916
Competitive Prices
Outstanding Workmanship
Johnson & Associates.....×○ 353-6623
'Your local plumber'
Jones Property Services.....○❑ 669-1302
Plumbing, all Maintenance
K & B, the Plumbing Experts×☆ 215-0401
KEYSTONE Plumbers.....☆○ 750-3867
Professional, Water Softeners
Kingmasters - Plumbing.....○× 507-3912
The Homeowners Friend
Liberty Bell Plumbers.....×○ 216-4207
'Freedom from Plumbing Problems'
Lloyd's Heating, Electric & Plumbing...○× 441-4095
M & R Plumbing.....❑○ 218-9270
'No Monkey Business'
MacKay Construction.....○❑ 782-0459
'Where the professionals work'
MARR, Tony & Sons,.....☆○ 965-6303
Over 5000 satisfied customers
Master Plumbers.....×× 322-8684
"Satisfaction Guaranteed"
Matthew Webber, Plumber...○× 434-0458
Top-flight Work at Fair Prices
Morelle & Partners.....○○ 544-1876
Lo Hourly Rate, Free Estimates
Morgan & Sons.....❑☆ 279-4188
Mobile Phone to Plumber 683-9875
Morris Johnson, Plumber.....☆❑ 698-0083
'An Early Response'
Max Keating.....○○ 487-6148
Put Plumbing Problems Behind you Today
National Plumbing & Heating○❑ 604-0608
Known Throughout the Country
NAUTILUS Plumbing.....❑○ 218-9216
Harry Green & Sons
Neat Plumb.....○☆ 645-6269
Joe & Tom Barker
Quick, Clean, Reasonable
NEPTUNE Plumbers.....×× 218-2217
Kitchens, Bathrooms
Start your Remodelling with Us
New Dimensions.....❑× 654-7403
Safe, Modern Plumbing
Norristown Contractors.....×○ 764-3206
'The Plumbing Experts'
Oakhouse Plumbers.....×○ 604-1112
All Appliances Installed

O'Brien and Sons
A Family Business
Olympic Plumber
Bathrooms, Kitche
PG Plumbing & E
Park Avenue Plu
Expert Repair Ser
Excellent Range o
Parkside Contrac
Installation, Plumb
Paul, The Plumbe
All Jobs Guarantee
Paul Drayton, Plu
7 Days a Week
Phoenix Plumber
You Can Have Co
Plumb Center.....
Regency Shoppin
Plumb-Sure.....
Located in the Libe
Plumbing Specia
Ray and Ed Brown
Poly Plumbers....
Merchants for All F
QUIK-SOLVE PL
Recommendations
RAINBOW PLUM
"The best in town"
Reynolds, A., Plu
"Do you know a go
(our customers do
Robertson, P. D.
Established for 15
ROCKWELL Plur
"Your Job Done R
Rollins Plumbing
Est. 1975, Free Es
Russell, Tom, Plu
Specialist in Water
Ryan Plumbing...
'Put your Pipes in
say "Good-bye"
SBJ Property Ma
Sabre Plumbing..
'We Have the Edg
Sam Wood's, Plu
General Skilled
Telephone Advice
Sargents Plumbi
Sound Advice for
SEARLE Plumbir
If we can't fix it, no
Call us for fast/free
Stanford & Sons.
Call on Us for Care
STAR Plumbers..
We Take Pride in F
STOP-DRIP.....
Careful, Courteou
SUNSHINE Plum
Domestic, Comme
"Large or small, we

iii) **Telephone task** (patient identifies pairs of symbols using the card below and an alternative card)

iv) NART word card (patient reads the following words aloud)

chord	___	thyme	___	aeon	___
ache	___	heir	___	placebo	___
depot	___	radix	___	abstemious	___
aisle	___	assignate	___	detente	___
bouquet	___	hiatus	___	idyll	___
psalm	___	subtle	___	puerperal	___
capon	___	procreate	___	aver	___
deny	___	gist	___	gauche	___
nausea	___	gouge	___	topiary	___
debt	___	superfluous	___	leviathan	___
courteous	___	simile	___	beatify	___
jaunty	___	banal	___	prelate	___
eqiuvocal	___	quadruped	___	sidereal	___
naive	___	cellist	___	demesne	___
catacomb	___	facade	___	syncope	___
gaoled	___	zealot	___	labile	___
		drachm	___	campanile	___

Appendix 4: Further information on neuropsychological tests

Table of orientation of test score directions

Neuropsychological test	Direction of score	Direction of follow-up minus baseline score	Direction of ranks of follow-up minus baseline score
MMSE	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Logical memory test (immediate, raw)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Logical memory test (immediate, %)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Logical memory test (delayed, raw)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Logical memory test (delayed, %)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Rey (copy)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Rey (recall)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Map (left, 1st minute)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Map (right, 1st minute)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Map (left, 2nd minute)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Map (right, 2nd minute)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement

Neuropsychological test	Direction of score	Direction of follow-up minus baseline score	Direction of ranks of follow-up minus baseline score
Map (total)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Telephone task (no. of targets)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Telephone task (time taken)	Low is good	Negative is improvement	Negative rank = improvement Positive rank = deterioration
Telephone task (dual task decrement)	Low is good	Negative is improvement	Negative rank = improvement Positive rank = deterioration
NART (no. of errors)	Low is good	Negative is improvement	Negative rank = improvement Positive rank = deterioration
NART (IQ)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
Digit span	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
PASAT (2.4-seconds)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement
PASAT (1.2-seconds)	High is good	Positive is improvement	Negative rank = deterioration Positive rank = improvement

Table of Cognitive domains and anatomical areas for the CAFE battery

Neuropsychological Test	Cognitive Domain	Anatomical Area
Logical Memory immediate (Raw and %)	Verbal short-term memory	Left hemisphere
Logical Memory delayed (Raw and %)	Verbal short-term memory	Left hemisphere
Digit Span	Verbal short-term memory	Left hemisphere
Map 1	Visual selective attention	Subcortical and cortical brain regions, anterior cingulate gyrus of frontal lobe (target detection, inhibition/ selection), right cerebral hemisphere (alertness/ maintenance)
Map 2	as above	as above
Map 3	as above	as above
Map 4	as above	as above
Rey Complex Copy	Non verbal memory	Right hemisphere
Rey Complex Delayed	Non verbal memory	Right hemisphere
National Adult Reading Test (Errors and IQ)	Premorbid intelligence	Left hemisphere (language)
Mini Mental State Examination	General cognitive function	-
Telephone task 1 (no. of targets)	Selective attention	Anterior circulate gyrus of frontal lobe (+/- subcortical region) of right hemisphere
Telephone task 2 (time taken)	as above	as above
Telephone task 3 (dual task decrement)	Divided attention	as above
Paced Serial Addition Test (2.4-seconds)	Information processing and attention	as above plus left hemisphere
Paced Serial Addition Test (1.2-seconds)	as above	as above

Appendix 5: GP Checklist

UNIVERSITY OF NEWCASTLE

C.A.F.E. *Cognition and Atrial Fibrillation Evaluation - a study of silent cerebral infarction and cognitive decline in AF)*

Checklist for New Practices

Consent form signed?

Has information on study given to

- **practice manager**
- **all partners**
- **all practice nurses?**

If labels to be used, has info been given to all using labels (as above)?

- **practice manager**
- **all partners**
- **all practice nurses?**

Practice info collected?

- **List size _____**
- **Number of fulltime partners_____**
- **Number of part-time partners_____**
- **Number of practice nurses_____**
- **Fully computerised_____**
- **Partially computerised? – to what extent_____**
- **Warfarin monitoring done where – pharmacist led/ GP/ hospital**

  _____

Further information on practice_____

_____

_____

Appendix 6: Consent form for GPs

UNIVERSITY OF NEWCASTLE

Silent Cerebral Infarction and Cognitive Decline in Atrial fibrillation Study

General Practitioner Consent Form

Name: Dr _____

Practice: _____

- Have you read the information sheet provided?
  YES / NO

- Have you had the opportunity to ask questions and discuss the study?
  YES / NO

- Have you received satisfactory answers to all your questions?
  YES / NO

- Have you received enough information about the study?
  YES / NO

- Who have you spoken to? _____

- Do you understand that your patients are free to withdraw from the study at any time without affecting your future medical care?
  YES / NO

- Do you agree to allow us to access patient's notes and records and select patients (who we will then invite to take part in the study)?
  YES / NO

Signed:_____ Date ___/___/_____

Witness:_____

Appendix 7: Letters to participants

i) Letter to controls

(SRH headed paper)

GP's name and address

Dr Helen Park

Department of Medicine for the Elderly,
School of Clinical Medical Sciences
Sunderland Royal Hospital
Kayll Road,
Sunderland
SR4 7TP
Telephone 0191 565 6256
Or 0191 222 7446

Dear (title, surname),

Re Atrial fibrillation and cognitive decline: a study of memory problems in older people

The University of Newcastle and Sunderland Royal Hospital are working with your GP to find out about memory problems in older people. We are trying to find out about whether or not there is a connection between the heart and memory problems. We are writing to ask for your help with this important work, which we hope will eventually allow doctors to prevent some memory problems from happening.

We are inviting people from your practice and other local practices to help us, not because there is anything wrong with their hearts, but because we want to know about everyone in the community, whether they are ill or not. We have used the list of patients registered with the practice to choose who to invite.

If you are happy to be involved with the study, one of the team here (either Dr Park or the team nurse) would like to visit you at home in order to go through a few questions about your health. We would like to carry out some simple memory tests. We would also like to check your blood pressure and perform an electrical tracing of your heart called an ECG (which stands for electrocardiogram). This test is very routine and certainly will not cause you any discomfort. We would also like to take a blood test. The visit will take one to two hours of your time.

After this visit, it may also be useful to do other tests of the heart and brain, which we will contact you about after the visit.

We will keep all of the information that you give us confidential. Your individual details will not be identifiable in any way in any reports arising from the study. However, we should like to send the results of your tests to your general practitioner. The information in the tests may be helpful to your own doctor as a general health check.

A suggested date and time when either Dr Park or the team nurse would like to visit is given on the sheet with this letter. We hope that this will be convenient for you. Please get in touch with Dr Park at the telephone numbers or address given at the head of this letter if the time is inconvenient, so that we can make other arrangements for you.

Please get in touch you have any questions, worries or if there is any reason why you do not wish to take part in the study. There is no obligation to take part. If you decide you do not want to help with the study this will not affect any care you receive from your GP.

However, it is important for the study that everyone from the invitation list can take part if they are able to, and we are very grateful for your help.

Yours sincerely,

Signature and name of GPs in the practice

Dr Helen Park

Signature

ii) Letter to cases

(SRH headed paper)

GP's name and address

Dr Helen Park

Department of Medicine for the Elderly,
School of Clinical Medical Sciences
Sunderland Royal Hospital
Kayll Road,
Sunderland
SR4 7TP
Telephone 0191 565 6256
Or 0191 222 7446

Dear (title, surname),

Re Atrial fibrillation and cognitive function: a study of memory problems in older people

The University of Newcastle and Sunderland Royal Hospital are working with your GP to find out about memory problems in older people. We are trying to find out about whether or not there is a connection between the heart and memory problems. We are writing to ask for your help with this important work, which we hope will eventually allow doctors to prevent some memory problems from happening.

We are inviting people from your practice and other local practices to help us. We are particularly interested in talking to healthy people who have an irregular heart beat (known as 'atrial fibrillation' or 'AF'). We have used the list of patients registered with the practice to choose who to invite.

If you are happy to be involved with the study, one of the team here (either Dr Park or the team nurse) would like to visit you at home in order to go through a few questions about your health. We would like to carry out some simple memory tests. We would also like to check your blood pressure and perform an electrical tracing of your heart called an ECG (which stands for electrocardiogram). This test is very routine and certainly will not cause you any discomfort. We would also like to take a blood test. The visit will take one to two hours of your time.

After this visit, it may also be useful to do other tests of the heart and brain, which we will contact you about after the visit.

We will keep all of the information that you give us confidential. Your individual details will not be identifiable in any way in any reports arising

from the study. However, we should like to send the results of your tests to your general practitioner. The information in the tests may be helpful to your own doctor as a general health check.

A suggested date and time when either Dr Park or the team nurse would like to visit is given on the sheet with this letter. We hope that this will be convenient for you. Please get in touch with Emma Hutchinson on 0191 222 5425 if the time is inconvenient, so that we can make other arrangements for you.

Please get in touch if you have any questions, worries or if there is any reason why you do not wish to take part in the study. There is no obligation to take part. If you decide you do not want to help with the study this will not affect any care you receive from your GP.

However, it is very important for the study that everyone from the invitation list can take part if they are able to, and we are very grateful for your help.

Yours sincerely,

On behalf of the partners at X GP practice

Signature

Dr Helen Park

Signature

iii) Shortened letter

GP name
GP address

Dr Helen Park
Department of Medicine for the Elderly
Sunderland Royal Hospital
Kayll Road
Sunderland SR4 7TP
Telephone 0191 565 6256 ext 42

Or 0191 222 7182

Date

Dear _____

Re The CAFÉ study: a study of memory problems in older people

About the study: We are performing a large research study about memory in older people, to find out whether there is a connection between the heart and people's memory. You may have seen our poster in Dr _____'s waiting room.

We would like to ask for your help with this important work, which may eventually allow doctors to prevent some memory problems from happening.

What we need from you: If you agree to be involved, one of us (either Dr Park or the team nurse) would visit you at home to go through some questions about your health including some memory questions, and carry out a short health examination including a blood pressure check. The visit will take one and half hours of your time.

We would like to take a blood test at the visit. However, we would still like you to be involved, even if you would prefer not to have the blood test. We would also like to do a scan of the heart at a later date, but we would still like you to be involved, even if you would prefer not to have this test. All of the information that you give us will be strictly confidential. However, we will send the results of your tests to your general practitioner for his/her records.

What happens now?

We hope that you will be able to help us. If so, please complete the reply slip enclosed and return it to us in the addressed envelope (stamp not needed). We will then contact you to arrange a convenient time for Dr Park or the study nurse to visit you at home.

We are very grateful for your help.

Yours sincerely,

Dr Helen Park On behalf of the partners at GP practice

iv) Reply slip

REPLY SLIP

If you are willing to help us with any part of this study, please tick the box and return this slip in the envelope provided (stamp not needed) as soon as possible. We will then contact you to arrange a convenient time to visit you at home.

- I am interested in being involved in the study ☐

Name
Study ID

Please write here the phone number at which you may be contacted

.....

If you have any questions about this form or any part of the study, please ring Dr Helen Park, telephone: 0191 222 5425

Thank you for your time

v) Letter to general practitioners

Headed paper
Date
GP name and address

Dear Dr _____

Re Silent cerebral infarction and cognitive impairment in atrial fibrillation study

We wish to explore a possible link between cognitive impairment and atrial fibrillation (AF), and are seeking your help.

Background

Several small studies have reported an association between cognitive decline and AF, including a pilot study by Dr O'Connell and Professor Gray. If this is indeed the case, it has important consequences for treatment and prevention. However, there are no prospective studies using detailed neuro-imaging (e.g. MRI).

We intend to carry out such a study in Sunderland. We have received ethical approval from Sunderland LREC and funding for a Regional Fellowship from NHS R&D.

Why we need your help

We need help to identify patients with NVAF and controls who we will assess prospectively with standardised measures of cognitive function and relevant investigations (including echo and MRI brain scan).

The project will involve access to patient notes to identify cases and controls. If you agree to be involved, we will help your practice to identify patients with AF using a combination of digoxin screening and opportunistic pulse palpation, perhaps supported by note flagging. We would then seek your permission to approach and consent patients. We would visit at home, and some will also be invited to Sunderland Royal Hospital for investigations.

The results of all investigations will be made available to you.

The team

- Dr Janice O'Connell: Department of Geriatric Medicine, School of Clinical Medical Sciences, University of Newcastle upon Tyne / Sunderland Royal Hospital
- Professor Richard Thomson: Department of Epidemiology and Public Health, University of Newcastle upon Tyne

- Professor Christopher Gray: Department of Geriatric Medicine, School of Clinical Medical Sciences, University of Newcastle upon Tyne / Sunderland Royal Hospital
- Mr Tony Hildreth: Medical Statistician, City Hospitals Sunderland
- Dr Helen Park: Research Training Fellow and Study Co-ordinator, University of Newcastle upon Tyne / Sunderland Royal Hospital

We hope you will be able to help with this study. We will telephone you at the surgery in two weeks time in order to discuss this with you further, but in the meantime please contact Dr Helen Park (telephone 0191 222 7182 or 0191 565 6256 ext 41243) if you have any queries.

Many thanks for your help with this study.

Yours sincerely,

Dr Helen Park

Dr Janice O'Connell

Professor Richard Thomson

Professor Christopher Gray

CAFÉ NEWSLETTER

UNIVERSITY OF NEWCASTLE

Department of Clinical Geriatrics, Sunderland Royal Hospital, Sunderland

Volume 1, Issue 7

May 2002

Dear Colleague

Many thanks for your continued help with the CAFÉ (Cognition and Atrial Fibrillation) study.

Update:

We have just reached the end of the one-year follow-up visits, carried out in the patient's own home. We appreciate your help in putting across to your patients the importance of this research in terms of preventing dementia in the future.

The majority of patients seemed to enjoy the follow-up visit and were interested in the study's progress. (Note: the follow-up visit consisted only of a repeat of the 'memory quiz' and health questionnaire; there was no ECG / examination/ blood test at this visit).

The CAFÉ team wish to thank all of the GPs, practice managers and other practice staff involved for your continued help with the study.

CAFÉ statistics: Practices involved : 44

Patients who have completed baseline: 362

Patients who have completed follow-up: 307

Dissemination of the results:

The baseline data has been analysed and we are currently in the process of writing up these results for publication. We will inform you once this has been finalised.

Once all of the follow-up data has been entered into our database we will begin this analysis, which will be ongoing over the summer months.

In addition to publication in journals, we intend to disseminate CAFÉ results through presentation at conferences in the UK. We will be taking a poster to the Annual Scientific Meeting of the Faculty of Public Health Medicine in June 2002 and we are in the process of submitting abstracts to other relevant meetings within the fields of geriatric medicine and public health medicine.

We will keep you up-to-date with any publications as they arise.

Contact details:

Dr Helen Park
c/o Dr O'Connell's secretary
Department of Medicine for the Elderly,
Health
Sunderland Royal Hospital
Kayll Road
Sunderland SR4 7TP
Tel: 0191 5656256, leave a message with Dr O'Connell's secretary

OR
Emma Hutchinson
Department of Epidemiology and Public

The Medical School
University of Newcastle
Newcastle upon Tyne NE2 4HH
Tel: 0191 2227182

vii) Poster for GP surgery waiting rooms

CAFÉ—A study of memory problems in older people

Dept of Clinical Geriatrics, Sunderland Royal Hospital, Sunderland

What is the Café Study?

This practice is involved with work being carried out by Sunderland Royal Hospital and the University of Newcastle, working with older people in the Sunderland area.

We are trying to find what may cause memory problems as people get older, so that ultimately we may help to prevent memory problems.

We need your help:-

To do this we need people aged over 60 years who have a reasonable memory. We are working with your GP to identify people, and you may receive a letter asking for your help. If you receive a letter, please help!

CITY HOSPITALS SUNDERLAND

WHAT DO I NEED TO DO?

If you receive a letter please return the reply slip and we will then visit you at home to go through a general health check and memory quiz.

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Appendix 8: Patient information leaflet

Taking part in research – a Patient Information Sheet

Study Title: Silent Cerebral infarction and Cognitive impairment in atrial fibrillation – a study of memory changes in people with or without an irregular heartbeat.

You have been asked to take part in a research project looking at memory changes in older people. Here is some information to help you to decide whether or not to take part. Please take time to read the information carefully and discuss it with relatives, friends and your GP if you wish. Ask us if there is anything you do not understand or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Do I have to take part?
Your participation is entirely voluntary and if you decide not to participate this will not affect your future medical care. If you do take part, you can still withdraw at any stage during the study without having to give a reason and again this will not affect your future care.

Why is the study being carried out?
It is possible that an irregular heartbeat, without treatment, could be linked with poorer memory in older people. If this is true, some memory problems could be prevented by good use of treatment for an irregular heartbeat. We want to test this theory by looking closely at different aspects of memory and brain function in a large number of people, some of whom have an irregular heartbeat. You have been chosen randomly as one of this large group of 480 people in the Sunderland area.

Who is organising the study?
A team based at Sunderland Royal Hospital and the medical school at Newcastle University is carrying out the study. The funding for the study is partly from the Northern and Yorkshire Regional Research and Development Directorate, and partly from other sources. The study is taking place over a period of 3 years.

What will happen to me if I take part?
If you do take part in the study one of the team will visit you at home at a time/date, which is convenient for you. You will be asked to answer some questions about your general health. You will also be asked to answer some detailed questions about memory and carry out a memory quiz. If you are willing, a small blood sample, blood pressure reading and harmless tracing of the heart (ECG) will be carried out - however, we would still like you to be involved in the study, even if you do not wish to have these, and would prefer to simply go through the interview and memory quiz.

At a later date you may be asked to attend Sunderland Royal Hospital for a harmless scan of the heart called an echocardiogram, which is similar to ultrasound scans of pregnant women. This will not affect your ability to drive, your diet, or any other aspect of your life. We would still like you to be involved in the study, even if you would prefer not to have the echocardiogram.

One year later we will visit you at home again, to go through the same questions and memory quiz (there will be no blood test or heart tracing).

What type of study is it?
This will be an 'observational study', which means that no drugs or new treatments are being used, i.e. we will simply be *observing* people in the study over the course of one year.

Possible risks
There are risks involved in this study that are minor – there may be slight bruising to the forearm after the blood sample has been taken. Otherwise, all of the tests are harm-free.

Insurance policies: as in all health checks, we will be measuring your blood pressure – if we detect high blood pressure, this occasionally has an affect on private medical insurance policies. If you have such a policy you should let the insurers know and they will be able to tell you whether this affects your insurance or not.

Possible benefits
You will receive a thorough health check, and any problems picked up can be passed on to your GP so that appropriate treatments can be started.

In the future, the information that we get from the study may help to reduce the chance of memory problems in people with an irregular heartbeat.

It is possible that the tests and questions may uncover some health problems unrelated to the study. We will pass on all information (confidentially) to your GP, so that he/she can treat you appropriately.

You will be told if important new information about this study becomes available which might affect your willingness to continue taking part. If at any time we consider it in your best interest, we will withdraw you from the study. We will then explain the reasons.

Payments
Sunderland Royal Hospital and the Newcastle University will be provided with funds from the grant-giving bodies, to contribute towards the overheads involved in carrying out the study.

GP notification
Your GP has helped us to find people to be involved in the study; therefore he/she is aware that you have been asked to take part. With your permission, we will pass on the GP your answers to the health-check questions and the results of your tests.

Restrictions
Taking part in the study will not restrict your diet, or affect whether or not you can give blood.

What if something goes wrong?
In the unlikely event that you are harmed by taking part in the study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Confidentiality – who will know I'm taking part in the study?

We will keep all the information (including test results) strictly confidential. Medical records of results relating to the study will not be disclosed to any third party other than your GP. We will ensure that we comply with any national data protection regulations.

What will happen to the results of the study?
We will publish the information from the study in medical journals, so that they are available to doctors, nurses and other relevant health professionals. These publications will include no reference to individual patients.

For more information:
Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

If at any time you have any questions about the study, or your rights as a participant, you should contact:

Dr Helen Park on telephone 0191 565 6256 ext 42109; or 0191 222 5425.

Thank you very much for taking part in this study.

Appendix 9: Table of definitions used in CAFÉ

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Study ID	A unique number assigned to each case and control		Numbers are assigned as patients are included in the study at the stage of GP note searching	n/a	n/a
GP record number	The patient's identification number used by a practice to access their computer records.		The number used to draw up patient records on the practice computer system. Although this number is unique within the practice, patients from different practices may have the same GP record number by chance.	Practice computer system	n/a
Name	Patient's full name	GP records	Surname, Forename	GP records	n/a
Age	n/a	n/a	The person's age in years at time of searching GP records, calculated automatically by database when date of birth is entered	Date of Birth from GP records, confirmed at interview with patient.	
Address	n/a	n/a	Full postal address	GP records	n/a
GP's name	Name of general practitioner responsible for the patient's care		Surname of senior partner in the practice	Database of senior partners (obtained from discussion with the then Health Authority for practices 1-10, from the practice itself thereafter	

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Caseness	Case is a patient included in the study, who fulfils the inclusion criteria and fails to meet any of the exclusion criteria		whether 'case' or 'control', if control, the study ID of the matched case is also recorded	n/a	n/a
Non valvular atrial fibrillation (NVAF)	chronic AF not caused by valvular heart disease	n/a	Whether NVAF or not, duration of NVAF, date of diagnosis, whether chronic or paroxysmal, treatment for NVAF, investigations for NVAF	GP notes	n/a
Coronary Heart Disease i) MI	'Myocardial infarction' in notes	Framingham	Only the number of MIs which had been noted, either GP in the records, or by secondary care doctors in their letters to GPs, were recorded in the database.	Hospital letters following acute treatment or follow-up of patient's myocardial infarction.	GP notes or GP letters recording MI as part of past medical history

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Coronary Heart Disease ii) Angina	Symptoms: brief, recurrent chest discomfort of up to 15 minutes, precipitated by exertion or emotion and relieved by rest or nitroglycerine. Definition is fulfilled if GP records or hospital letters which record 'angina' are consistent with the symptoms in this definition, providing appropriate investigations (e.g. exercise ECG) do not dispute this. Note exercise-induced shortness of breath may also be a presenting feature of angina (but in patients with COPD the notes may not discriminate between the two possible aetiologies).	Framingham	Only whether angina (as defined) is present or absent. If present, whether the patient is currently on treatment for angina is also documented. Treatment for angina is defined as any drug noted as being for the management of an acute angina attack (e.g. nitroglycerine) or as angina prophylaxis (e.g. B-blockers, nitrates, calcium antagonists). 'Currently on treatment is defined as the drug being on repeat prescription at the time of GP note searching, or where repeat prescription lists are not available /used, the drug being prescribed such that the patient has access to continuous supply of the drug since it was commenced to the time of GP notes searching.	GP computerised medication record in 'repeat medication' section	GP consultation notes which mention drugs prescribed, hospital letters. It may have been unclear from the notes as to the indication for some drugs (e.g. frusemide, B-blockers). At interview the patient should be asked to confirm if possible, the disease indication for such drugs. If there is a conflict between patient and good, clear GP records, the information from GP records should be accepted in preference.

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Hypertension	Systolic blood pressure greater than 160 mmHg, diastolic blood pressure greater than 95mmHG. BP recorded twice - if either of the first readings or either of the second readings is raised to these levels, hypertension is noted. In addition, any patient on anti-hypertensive medication is noted as hypertensive. Also see British Hypertension Society guidelines [1]	Framingham	After interview and before physical examination (patient has been sitting for around 50 minutes - 1 hour), 2 consecutive blood pressure readings taken one minute apart, all both recorded. Taken with patient sitting, arm resting on table, sphygmomanometer at level of heart. In addition, when screening notes, record made of whether there is a GP diagnosis of hypertension, if yes, whether or not patient is receiving medication for hypertension, if no, was there a previous record of medication for hypertension	For BP readings: Patient visit 1A (baseline visit) For history of hypertension: GP notes	n/a

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Stroke	Rapidly developing clinical signs of focal, or at times global, disturbance of cerebral function; with symptoms lasting longer than 24 hours(unless due to an intracerebral/subarachnoid haemorrhage) or leading to death; with no apparent cause other than that of vascular origin.	WHO	GP notes: record of ever stroke or ever TIA	GP notes	Patient visit 1A (baseline visit) Follow-up visits
Probable TIA	As above, resolving with 24 hours	WHO	As above	GP notes	Patient visit 1A (baseline visit) Follow-up visits
Diabetes	If the patient is under treatment by a physician for diabetes – i.e. they are taking insulin or oral hypoglycaemic agents.	Framingham and British Diabetic Association (www.diabetes.co.uk)	GP notes: whether the patient has a GP record of diabetes (type I or type II), medication taken for diabetes. Non-fasting blood glucose taken at baseline visit	History of diabetes: GP notes; Blood glucose: baseline visit	N/a

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
	If they are taking oral agents diagnosis made only if supported by several elevated blood glucose determinants before treatment started **Or** The patient has a record of an abnormal glucose tolerance test or at least two causal blood glucose determination tests of 150mg/ml or more. **Or** The patient is under treatment for diabetes controlled with diet alone and the diagnosis is supported by appropriate abnormal glucose tolerance test or raised fasting blood glucose.				

Feature of database	Definition	Source of definition	Exactly what data is collected?	Preferred Source	If Preferred source not available, alternative source?
Congestive Heart Failure	Shortness of breath causing: i) no limitation of activity ii) some	NYHA classification	Information from GP notes regarding symptoms of shortness of breath due to CHF (attempting to differentiate this from other causes of shortness of breath for example COPD). Information gathered in line with NYHA classification	GP notes, Baseline interview, Follow-up interview	n/a
Oedema	Clinically apparent increase in the interstitial fluid volume. *Or* swelling of the tissues due to interstitial fluid	Harrison's Principles of Internal Medicine, Mc Leod	Patient asked question on ankle swelling (attempt to differentiate from dependant oedema) and examination included note taken of presence/absence of oedema	Baseline and follow-up interview, examination	N/a
Dementia	GP record of diagnosis of dementia, if possible supported by letter from old age psychiatrist. (Also MMSE <24 at baseline interview)	DSM-IV	Information from GP notes on diagnosis of dementia or not. MMSE at start of interview	GP notes, Baseline interview Follow-up visits	n/a
Smoking	Patient placed in one of the following categories		Questions on smoking as part of the health questionnaire at baseline interview	Baseline interview	n/a

Appendix 10: GP notes exclusion checklist

General Information	
GP records number	
Name	
Case or control	
Aged over 60? *If no = excluded*	

Cases only:

AF	
Currently has AF? *If no = excluded*	
Currently has chronic AF? *If no = excluded*	
Was diagnosis made before January 1995? *If yes = excluded*	

Cases and controls:

Stroke	
Any record of the patient having a stroke (WHO criteria)? *If yes = excluded*	
Any record of the patient having a TIA (WHO criteria)? *If yes = excluded*	

Heart Failure	
If any symptomatic heart failure in the last 3 months, do notes state the following:	
• less than ordinary activity results in symptoms? *If yes = excluded*	
• any physical activity causes discomfort? *If yes = excluded*	
• symptoms are present at rest? *If yes = excluded*	

Severe visual or hearing impairment	
Do the records suggest that the patient has severe visual impairment *If yes = excluded*	
Do the records suggest that the patient has severe hearing impairment *If yes = excluded*	

Dementia	
Any record of the patient having established dementia? *If yes = excluded*	

Prosthetic valves/rheumatic fever:	
Any record of a prosthetic valve? *If yes = excluded*	
Any record of a pacemaker? *If yes = excluded*	
Any record of having suffered from rheumatic fever? *If yes = excluded*	

Other reason for exclusion in study? (*If yes, please state reason below)*	

Is patient excluded from study?	

If reason for exclusion not in list, please state here: -

_____

_____

_____

Appendix 11: Consent form for participants

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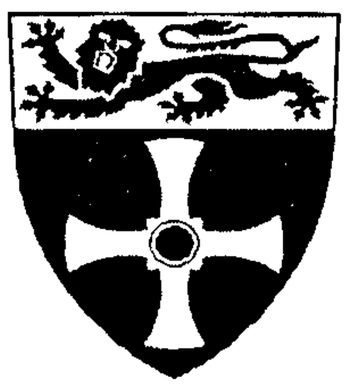

Department of Epidemiology
and Public Health

Atrial fibrillation and cognitive decline: a Study of Memory Problems in Older People: Patient Consent Form

Name: _____

- Have you read the patient information sheet or has this been read to you?
  YES/NO

- Have you had the opportunity to ask questions and discuss the study?
  YES/NO

- Have you received satisfactory answers to all your questions?
  YES/NO

- Have you received enough information about the study?
  YES/NO

- Who have you spoken to? _____

- Do you understand that you are free to withdraw from the study at any time without affecting your future medical care?
  YES/NO

- Do you agree to your GP being informed of your participation in the study?
  YES/NO

- Do you agree to take part in the study?
  YES/NO

Signed:_____ Date __/___/_____

Witness:_____Date___/___/_____
__

Appendix 12: Interview dataforms

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C.A.F.E.

(Cognition and Atrial Fibrillation Evaluation - a study of memory problems in older people)

Patient Visit 1: Interview Data-form (sections 1-10)

STUDY NUMBER | | | | | |

Study Details:

Tick when completed:

Interview ☐

Neuropsychological tests ☐

ECG done ☐

Bloods taken ☐

Blood results received ☐

Physical Examination ☐

Patient's status in study:

Case ☐

Control ☐

Excluded from study ☐

Included in study ☐

STUDY NUMBER | | | | | |

SECTION 1 - Personal details

Today's date: _____/_____/_____

1. Surname _____

2. Forenames_____ _____

3. Date of birth:

Day	Month	Year

2. Sex:

Male 1

Female 2

3. Marital status:

Single / Never married 1

Married 2

Widow / Widower 3

Divorced 4

Separated 5

Family history:

Is there a family history (mother, father , siblings)of :

4. Stroke? Yes 1 no 2

5. Heart attacks? Yes 1 no 2

6. Raised blood pressure? Yes 1 no 2

7. Memory problems, including dementia? Yes 1 no 2

STUDY NUMBER | | | | | |

SECTION 2 - Current Health Problems and Past Medical History

1. Have you ever had a stroke (sometimes known as cerebral haemorrhage, cerebral thrombosis, brain haemorrhage, subarachnoid haemorrhage, cerebrovascular accident (CVA) or a mini-stroke or TIA)? Yes **1*** No **2**

2. Have you recently noticed any of the following (excluding symptoms known to be due to migraine):

temporary weakness in one or both arms/ legs Yes **1*** No **2**
temporary numbness/ unusual feeling in a specific area of the body (including face) Yes **1*** No **2**
temporary visual problems (e.g. blurring in one eye, double vision) Yes **1*** No **2**
temporary slurred speech or other speech problem Yes **1*** No **2**

3. In the past month, have you experienced any of the following symptoms (interviewer - see protocol for details of information needed from this question):

shortness of breath:- Yes **1** No **2**

if yes, circle most appropriate:-

- no limitation of activity; ordinary activity does not cause symptoms **1**
- slight limitation of activity; ordinary activity results in symptoms **2**
- marked limitation of activity; less than ordinary activity results in symptoms **3**
- unable to carry out any physical activity without discomfort symptoms at rest. **4**

swollen ankles (consistent with oedema) Yes **1** No **2**

palpitations (consistent with arrythmia) Yes **1** No **2**

pain in the calves/thighs on walking (consistent with claudication) Yes **1** No **2**

fainting/dizziness Yes **1** No **2**

If yes = consider patient exclusion (see medical history exclusion protocol)

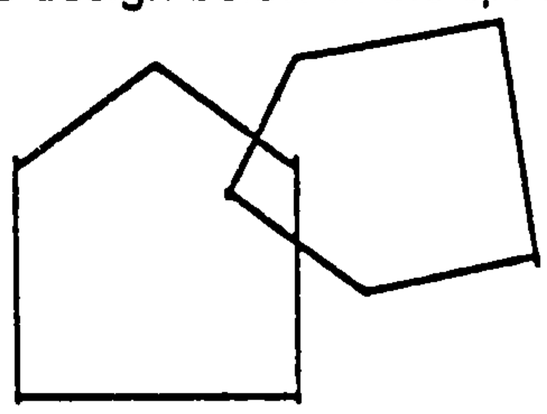
***Extra information** - e.g. if it is not clear whether symptom/ history is an exclusion or not, so to be discussed with rest of study tea, write details here:*

STUDY NUMBER | | | | | |

Section 3 - Mini mental state examination

Score		Orientation
3.1( )		what is the (year)(season)(month)(date)(day)? -5 pts
3.2( )		where are we (country)(county)(town)(hospital)(flr) -5 pt
		Registration
3.3( )		name 3 objects(PLATE,SHOE,CHAIR): 1 second to say each. Then ask patient to repeat all 3 after you have said them. 1 point for each correct. Then repeat them until he/she learns them. Count trials and record. - 3 pts
		Attention and calculation
3.4( )		serial 7's (100,93,86,79,72,65).1 point for each correct. Stop at 5 answers. Or spell ~~'WORD'~~ backwards. number correct equals letters before first mistake - i.e., dlorw = 2 correct). - 5 pts total "WORLD"
		Recall
3.5( )		Ask for objects above. 1 point for each correct. -3 pts
		Language tests
3.6( )		Name - pencil, watch - 2 pts
3.7( )		repeat - no ifs, ands or buts - 1 pt
3.8( )		follow a 3 stage command: "Take the paper in your right hand, fold it in half, and put it on the floor) - 3 pts
3.9( )		Read and obey the following (show separate sheet if necessary): **'CLOSE YOUR EYES'** 1 pt
3.10( )		Write a sentence spontaneously below - 1pt

3.11( ) Copy the design below in the space next to it. -1 pt



( ) **Total** max.=30 points ***(less than 24 = exclusion)***

3.12 Assess level of conciousness along a conintuum (make mark on line):

Alert *drowsy* *stupor* *coma*

STUDY NUMBER

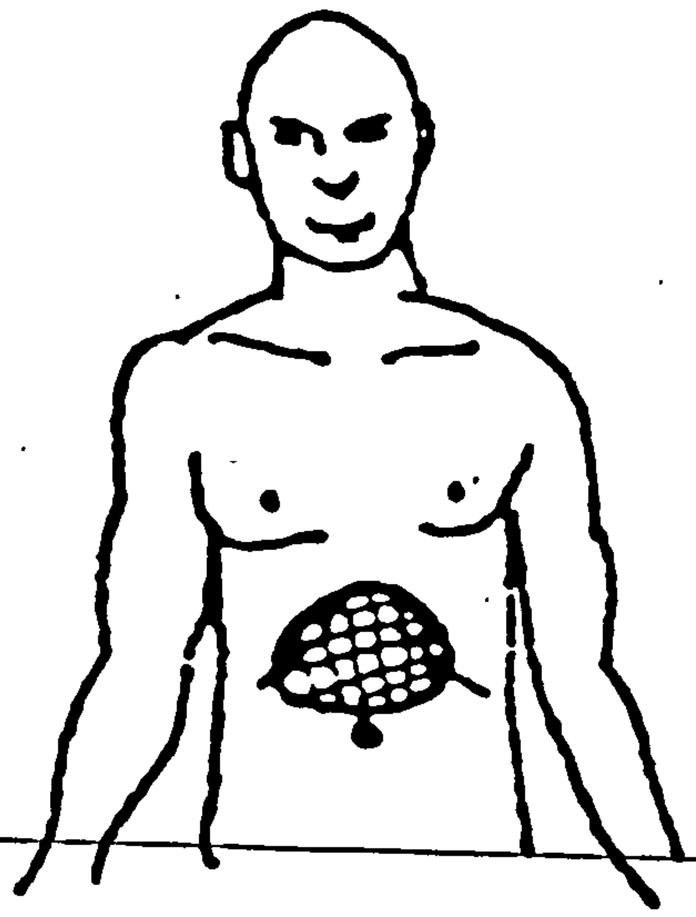
SECTION 4 - Contraindications to anticoagulation

4.1.Have you ever had indigestion for more than a few days?

Yes 1

No 2

4.2.Have you ever had pain or discomfort in the place shown in the picture, or excessive wind or fullness after eating or drinking?



Yes 1

No 2

Sketch

4.3.Have you ever had heartburn (discomfort or pain in the chest) after eating or drinking?

Yes 1

No 2

4.4Have you had any of the above symptoms in the last six months?

Yes 1

No 2

4.5Have you ever been diagnosed as having a gastric (stomach) or duodenal ulcer?

Yes 1

No 2

STUDY NUMBER | | | | | |

4.6.Have you ever had a barium meal examination? (You have to drink a white liquid before the X-rays are taken)

Yes 1

No 2

4.7.Have you ever had an endoscopy or gastroscopy? (A tube with a light source is swallowed to look inside the stomach)

Yes 1

No 2

4.8.Have you ever vomited (thrown up) any blood?

Yes 1

No 2

4.9.Have you vomited (thrown up) any blood **in the last six months?**

Yes 1

No 2

4.10Have you ever noticed any blood in your urine (water)?

Yes 1

No 2

4.11.Have you noticed any blood in your urine (water) **in the last six months?**

Yes 1

No 2

4.12.Have you ever noticed any blood in your faeces (motions, bowels)?

Yes 1

No 2

4.13.Have you noticed any blood in your faeces (motions, bowels) **in the last six months?**

Yes 1

No 2

STUDY NUMBER |_|_|_|_|_|

SECTION 5 - Medication

5.1.Do you **currently** take aspirin tablets **every day** or more often?

Yes 1
No 2

Only for those who currently take aspirin every day or more often:

5.2. Up to today's date, for how long have you been taking aspirin tablets for?

Months|_|_| Years|_|_|

5.3.Those taking aspirin - what dose of aspirin do you take? _____mg

5.4.Has there **ever** been any time in your life when you have taken aspirin tablets **every day** or more often?

Yes 1
No 2

5.5.Do you **ever** take aspirin tablets these days?

Yes 1
No 2

Only for those who have at some time taken aspirin every day or more often, but are not currently taking it:

5.6. For how long in total did you take daily aspirin?

Months|_|_| Years|_|_|

5.7.Why did you stop taking daily aspirin? _____

5.8.When did you stop taking daily aspirin? |_|_| |_|_|_|_|
Month Year

5.9.Do you currently take warfarin tablets?

Yes 1
No 2

STUDY NUMBER ☐☐☐☐☐

Only for those who currently take warfarin:

5.10.Up to today's date, for how long have you been taking warfarin tablets?

Months☐☐ Years☐☐

5.11.Has there **ever** been any time in your life when you have taken warfarin tablets? Yes **1** No **2**

Only for those who have at some time taken taken warfarin, but are not currently taking it:

5.12. For how long in total did you take warfarin?

Months☐☐ Years☐☐

For those who are taking or have ever taken warfarin, if the patient has an INR book available :

5.13. How many person years was the patient's INR within the following ranges:

<2.0_____person years

2.0 to 2.99_____ person years

3.0 to 3.99_____ person years

4.0 to 4.99_____ person years

<5.0_____ person years

5.14.List any other medication currently taken (ask patient to show the bottles):

Name of Drug	Dose	Indication

STUDY NUMBER | | | | | |

SECTION 6 - smoking and drinking

6.1.Which of the following best describes your **cigarette** smoking habits?

I smoke daily	1
I smoke occasionally, but not every day	2
I used to smoke daily, but do not smoke at all now	3
I used to smoke occasionally, but do not smoke at all now	4
I have never smoked	5

6.2.Do you currently smoke a pipe?

Yes	1
No	2

6.3.Do you currently smoke cigars?

Yes	1
No	2

Only for those currently smoking <u>cigarettes</u> every day:

6.4.About how many cigarettes (manufactured or hand-rolled) do you smoke each day? | |

6.5.How often do you drink alcohol?
(please include any night-caps you may take, or alcohol that you put in tea or coffee)

I drink alcohol every day	1
I drink alcohol on most days	2
I drink alcohol about 2 or 3 times a week	3
I drink alcohol about once a week	4
I drink alcohol once or twice a month or less	5
I used to drink alcohol regularly, but do not drink at all now	6
I used to drink alcohol occasionally, but do not drink at all now	7
I have never drunk alcohol	8

STUDY NUMBER | | | | | |

6.6. Have you had any of the following alcoholic drinks **since this time last week?**

Assume that one small can is half a pint, and please include night-caps or alcohol taken with tea or coffee.

Shandy (canned)	_____ pints
Shandy (mixed)	_____ pints
Beer or lager	_____ pints
Low alcohol beer or lager	_____ pints
Cider	_____ pints
Wine	_____ glasses
Low alcohol wine	_____ glasses
Martini, Cinzano, sherry, Babycham etc.	_____ glasses
Spirits (gin, whisky, vodka, rum, etc.)	_____ measures

Other (write how much and of what in box below)

STUDY NUMBER | | | | | |

SECTION 7 - views on your health/quality of life/psychological health

If not sure, give nearest possible answer.

7.1. In general would you say your health is:

(please circle one number)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

7.2. Compared to one year ago, how would you rate your health in general now?

(please circle one number)

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse than now than one year ago	4
Much worse now than one year ago	5

STUDY NUMBER _____

The following questions are about activities you might do during a typical day.

7.3.Does <u>your health now limit you</u> in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling or stooping	1	2	3
Walking more than a mile	1	2	3
Walking half a mile	1	2	3
Walking one hundred yards	1	2	3
Bathing or dressing yourself	1	2	3

7.4. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u>

(circle one number on each line)

	YES	NO
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the kind of work or other activities	1	2
Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

STUDY NUMBER | | | | | |

7.5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
Cut down on the **amount of time** you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as **carefully** as usual	1	2

7.6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(circle one number)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7.7. How much bodily pain have you had during the past 4 weeks?

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

7.8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

STUDY NUMBER | | | | | |

7.9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much during the past 4 weeks-

	All of the Time	Most of the Time	A Good Bit of The Time	Some of the Time	A Little of the Time	None of the Time
Did you feel full of life?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

7.10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

7.11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
I seem to get ill more easily than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

STUDY NUMBER

SECTION 8 - Educational level

We should like to know about your **present or last** job.

8.1. On the lines after **"Full job title"** please give the full title by which the job is known, for example: 'packing machinist; 'poultry processor'; 'jig and tool fitter'; supervisor of typists' 'accounts clerk'; rather than general titles like 'machinist'; 'process worker'; 'supervisor'; or 'clerk'. Give rank or grade if the person has one.

Full job title:

_____

_____

8.2. On the lines after **"Main things done in job"** please write down the main things you actually do or did in the job.

Main things done in job:

_____

_____

Armed forces- enter 'commissioned officer' or 'other rank' as appropriate at **"Full job title"** and leave the second section blank.

Civil servants- give grade at **"Full job title"** and discipline or specialism, for example 'electrical engineer'; 'accountant'; 'chemist'; 'administrator' at **"Main things done in job"**

8.3. At what age did you finish your continuous full-time education?

Not yet finshed	**1**
Never went to school	**2**
14 years or under	**3**
15 years	**4**
16 years old	**5**
17 years old	**6**
18 years old	**7**
19 years or over	**8**

STUDY NUMBER

8.4 Please look at this card and tell me whether you have passed any of the qualifications listed. Look down the list and tell me the first one you come to that you have passed.

Degree (or degree level qualification)	}	1
Teaching qualification	}	2
HNC/HND, BEC/TEC Higher, BTEC Higher	}	
City and Guilds Full Technological Certificate	}	
Nursing Qualifications (SRN, SCM, RGN, RM, RHV, Midwife)	}	
'A' levels /SCE Higher	}	3
ONC/OND/BEC/TEC **not** higher	}	
City and Guilds Advanced/Final level	}	
'O' level passes (grade A-C if after 1975)	}	4
GCSE (grades A – C)	}	
CSE Grade 1	}	
SCE Ordinary (Bands A-C)	}	
Standard Grade (Level 1-3)	}	
SLC Lower	}	
SUPE Lower or Ordinary	}	
School Certificate or Matric	}	
City and Guilds Craft/Ordinary level	}	
CSE Grades 2-5	}	5
GCE 'O' level (Grades D&E if after 1975)	}	
GCSE (Grades D,E,F,G)	}	
SCE Ordinary (Bands D &E)	}	
Standard Grade (Level 4,5)	}	
Clerical or commercial qualifications	}	
Apprenticeship	}	
CSE Ungraded	}	6
Other qualifications (**specify**)	}	7
No qualifications	}	8

STUDY NUMBER | | | | | |

Only for those who are married, or have been married:

We should like to know about the **present or last** job done by **your spouse.**

8.5. On the lines after **"Full job title"** please give the full title by which the job is known, for example: 'packing machinist; 'poultry processor'; 'jig and tool fitter'; supervisor of typists' 'accounts clerk'; rather than general titles like 'machinist'; 'process worker'; 'supervisor'; or 'clerk'. Give rank or grade if the person has one.

Full job title:

_____

_____

8.6. On the lines after **"Main things done in job"** please write down the main things your spouse actually does or did in the job.

Main things done in job:

_____

_____

Armed forces- enter 'commissioned officer' or 'other rank' as appropriate at **"Full job title"** and leave the second section blank.

Civil servants- give grade at **"Full job title"** and discipline or specialism, for example 'electrical engineer'; 'accountant'; 'chemist'; 'administrator' at **"Main things done in job"**

TEXT BOUND INTO THE SPINE

OGICAL MEMORY TEST

diate recall

STUDY NUMBER

RY 'A'

/ Thompson / of South / Gosforth ,/ employed / as a cook / in a school /cafeteria /

ted / at the High St /Police Station / that she had been held up / on Clarence Street / the

t before / and robbed / of fifty-six pounds. / She had four / small children, / the rent was

e,/ and they had not eaten / for two days./ The police, / touched by the woman's story;/

ok up a collection / for her./

ORY 'B'

obert / Miller / was driving / a ten-ton / lorry / down a road / at night / in the Norfolk /

roads, / carrying eggs to Norwich / , when his axle / broke. / His lorry skidded / off the

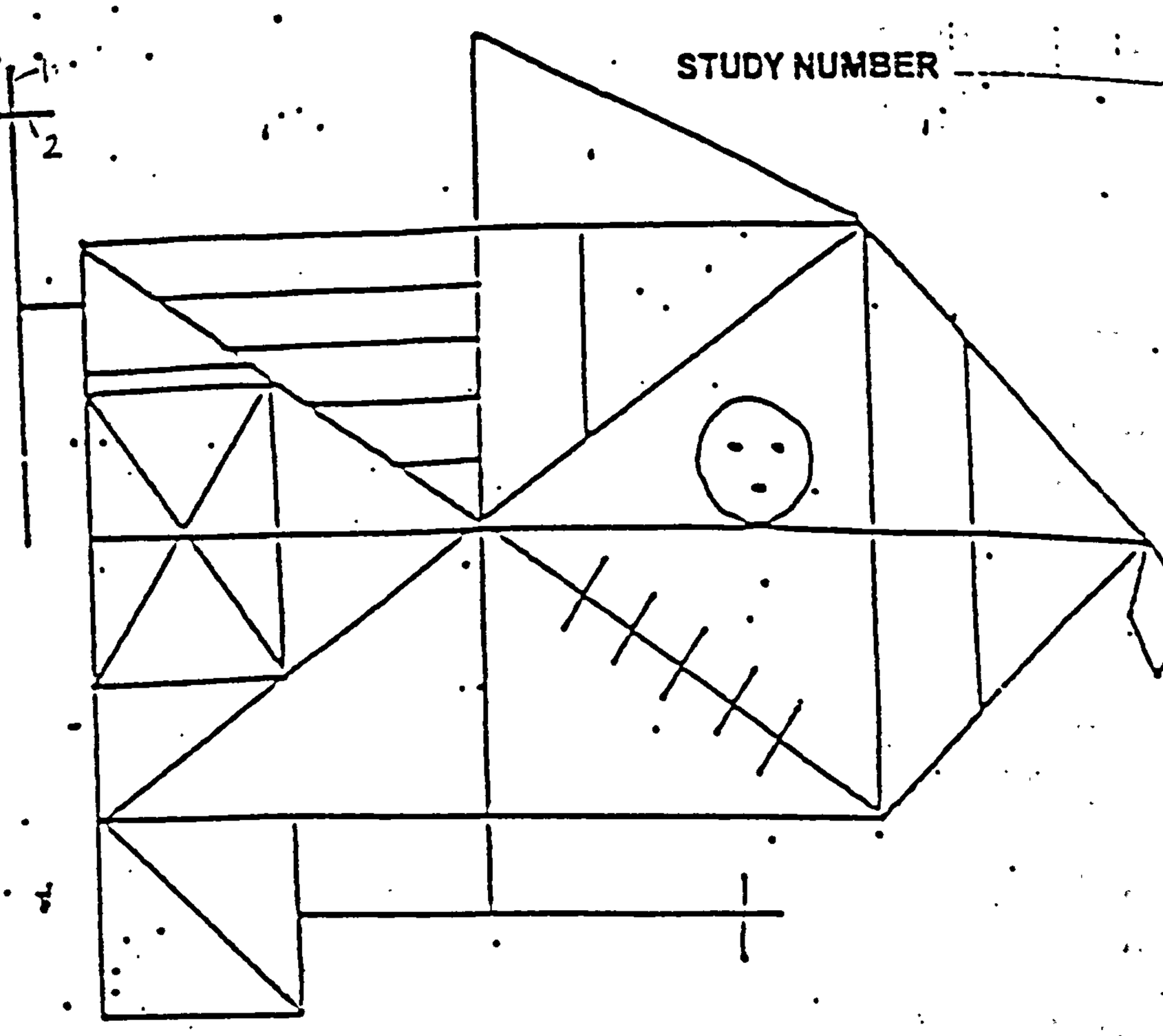
oad/ into a ditch. / He was thrown / against the dashboard / and was badly shaken. / There

was no traffic / and he doubted that help would come. / Just then his two-way radio / buzzed. /

He quickly answered. / " This is 12 ". /

STUDY NUMBER

3 (a) REY FIGURE COPY



3. REY FIGURE

STUDY NUMBER |_|_|_|_|

Copy

See separate sheet

Score (max. 36) |_|_|

4. TESTS OF EVERYDAY ATTENTION

MAP SEARCH TASK

Garage (screwdriver & spanner) OR petrol station (gas pump) symbols (Max. score 80)

1 minute (red pen)	left	|_|_|
	right	|_|_|
2 minutes (blue pen)	left	|_|_|
	right	|_|_|

5. TESTS OF EVERYDAY ATTENTION

TELEPHONE SEARCH

Single task (plumbers)

No. of correct targets (max. 20)	N	|_|_|
Time taken (seconds)	t	|_|_|_|_|
Time per target (seconds)	t / N = t_t	|_|_|_|_|

LEPHONE SEARCH

STUDY NUMBER

ıal task (restaurants)

ɔ of correct targets	N_1	
ime taken (seconds)	t_1	
ime per target $\left(\frac{t_1}{N_1}\right)$	$t\,t_1$	

COUNTING

Dual task counting
5 4 8 3 6 1 12 2
5 7 5 9 2 6 11 3
6 3 5
3 6 1 12 2 5 7 5
9 2 6 11 3 6 3 5
5 4 8
2 5 7 5 9 2 6 11
3 6 3 5 5 4 8 3 6 1 12

No of strings attempted	x	
No. correct	y	
Proportion correct	$y / x = p$	
Adjusted double score	$t_{t1} / p = z$	
Dual task decrement	$z - t_t$	

NATIONAL ADULT READING TEST

50 WORDS

STUDY NUMBER ____

Tick if correct:

chord	___	thyme	___	aeon	___
ache	___	heir	___	placebo	___
depot	___	radix	___	abstemious	___
aisle	___	assignate	___	detente	___
bouquet	___	hiatus	___	idyll	___
psalm	___	subtle	___	puerperal	___
capon	___	procreate	___	aver	___
deny	___	gist	___	gauche	___
nausea	___	gouge	___	topiary	___
debt	___	superfluous	___	leviathan	___
courteous	___	simile	___	beatify	___
jarcfy	___	banal	___	prelate	___
eqiuvocal	___	quadruped	___	sidereal	___
naivc	___	cellist	___	demesnc	___
catacomb	___	facade	___	syncope	___
gaoled	___	zealot	___	labile	___
		drachm	___	campanile	___

No. of errors ___

7. DIGIT SPAN

FORWARD	Pass-Fail	Score 2, 1, or 0		DIGITS BACKWARD	Pass-Fail	Score 2, 1, or 0
2			1	2-4		
4				5-3		
3-9			2	6-2-9		
8-5				4-1-5		
7-3-1			3	3-2-7-9		
2-3-5				4-9-6-8		
9-4-7-3			4	1-5-2-8-6		
2-4-8-7				5-1-8-4-3		
1-7-4-2-8			5	8-3-9-4-1-8		
7-3-3-8-6				7-2-4-8-5-6		
1-9-2-6-4-7			6	6-1-2-9-3-8-5		
2-9-5-1-7-4				4-7-3-9-1-2-8		
5-8-6-2-5-8-4			7	8-4-3-7-6-2-5-3		
3-9-4-2-5-6-8				7-2-8-1-9-6-5-3		

Max = 14

Total Forward *To*

TEXT CUT OFF IN ORIGINAL

b) LOGICAL MEMORY TEST

30 minute recall

STUDY NUMBER |_|_|_|

STORY 'A'

Anna / Thompson / of South / Gosforth. / employed / as a cook / in a school / cafeteria

reported / at the High St / Police Station / that she had been held up / on Clarence St / the

night before / and robbed / of fifty-six pounds. / She had four / small children. / the rent was

due / and they had not eaten / for two days. / The police, / touched by the woman's story, /

took up a collection / for her./

STORY 'B'

Robert / Miller / was driving / a ten-ton / lorry / down a road / at night / in the Norfolk /

Broads. / carrying eggs to Norwich. / when his axle / broke. / His lorry skidded / off the road

/ into a ditch. / He was thrown / against the dashboard / and was badly shaken. / There was no

traffic / and he doubted that help would come. / Just then his two-way radio / buzzed. / he

quickly answered. / "This is 12"./

3 (b) REY FIGURE

30 minute recall

See separate sheet

Score (max. 36) |_|_|

3 (b) REY FIGURE RECALL

STUDY NUMBER

NAME
DATE

8 (a) PASAT 2.4 SECONDS

STUDY NUMBER _____

o.	answer	no	answer	no.	answer	no	answer
		7	9	6	8	2	11
	9	8	15	3	9	3	5
	10	5	13	7	10	9	12
	7	9	14	5	12	7	16
3	12	4	13	8	13	4	11
1	9	2	6	3	11	5	9
5	6	9	11	9	12	7	12
6	11	7	16	1	10	6	13
( )	15	6	13	4	5	8	14
	10	5	11	8	12	1	9
3	4	8	13	6	14	3	4
6	9	1	9	2	8	1	4
1	10	4	5	7	9	9	10
3	7	1	5	5	12	2	11
2	5	2	3	9	14	5	7
						6	11

Raw score correct ...../ 60

8 (b) PASAT 1.2 SECONDS

no.	answer	no	answer	no.	answer	no	answer
2		7	9	6	8	2	11
7	9	8	15	3	9	3	5
3	10	5	13	7	10	9	12
4	7	9	14	5	12	7	16
8	12	4	13	8	13	4	11
1	9	2	6	3	11	5	9
5	6	9	11	9	12	7	12
6	11	7	16	1	10	6	13
9	15	6	13	4	5	8	14
1	10	5	11	8	12	1	9
3	4	8	13	6	14	3	4
6	9	1	9	2	8	1	4
4	10	4	5	7	9	9	10
3	7	1	5	5	12	2	11
2	5	2	3	9	14	5	7
						6	11

Raw score correct ...../ 60

STUDY NUMBER

Section 10 - Investigations

Bloodtests

Biochemistry

	result	Date of investigaton	day	month	year
Sodium					
Potassium					
Urea					
Creatinine					
Glucose					
HbAlc					
TSH					
Digoxin					
Cholesterol					

Haematology

Haemoglobin					
Haematocrit					
WBC					
Platelets					

CG

STUDY NUMBER

is AF in case? Yes 1 Confirms SR in controls? Yes 1
No 2 No 2

AF STUDY ECG CODING FORM (MINNESOTA CODE) STUDY NO. ___

ECG DATE ___/___/___ CODING DATE ___/___/___

1. Q & QS PATTERNS

Anterolateral site (I, aV_L, V6) 1 - ___ - ___

Posterior (inferior) site (II, III, aV_F) 1 - ___ - ___

Anterior site (V1 - V5) 1 - ___ - ___

2. FRONTAL PLANE QRS AXIS +/- ___ ^{0} 2 - ___

3. HIGH AMPLITUDE R WAVES 3 - ___

4. S - T JUNCTION (J) & SEGMENT DEPRESSION

Anterolateral site 4 - ___ - ___

Posterior site 4 - ___ - ___

Anterior site 4 - ___ - ___

5. T - WAVE ITEMS

Anterolateral site 5 - ___

Posterior site 5 - ___

Anterior site 5 - ___

6. A - V CONDUCTION DEFECT 6 - ___ - ___

7. VENTRICULAR CONDUCTION DEFECT 7 - ___ - ___

8. ARRHYTHMIAS 0 = normal, 1 = abnormal ___

Arrhythmia code (8-3-1 = AF) 8 - ___ - ___

9 - 2 S - T SEGMENT ELEVATION 0 = no, 1 = yes

Anterolateral site ___

Posterior site ___

Anterior site ___

9. MISCELLANEOUS CODES 9 - ___ - ___

MASTER

STUDY NUMBER | | | | | |

Private and confidential

UNIVERSITY OF NEWCASTLE

CITY HOSPITALS SUNDERLAND

C.A.F.E.

(cognition and atrial fibrillation evaluation - a study of memory problems in older people)

Patient visit 1a: physical examination data-form (section 11)

STUDY NUMBER |_|_|_|_|_|

nt's status in study:

ol	☐
ded from study	☐
ed in study	☐

ion 11.1 - personal details

udy id number (check against other records)

|_____|

te of birth(check against other records)

|_____|_____|_____|
day month year

<u>asic information</u>

Height _____m *or* _____feet_____inches

Weight_____Kg *or* _____stone _____pounds

BMI _____

Cardiovascular examination

11.4Pulse rate _____

rhythm regular 1
irregular 2

11.5Blood pressure systolic _____mmHg diastolic _____mmHg

11.6Pedal pulses present right Yes 1 left Yes 1
No 2 No 2

11.7Oedema Yes 1
No 2

11.8Raised JVP Yes 1
No 2

11.9Added heart sounds Yes 1
No 2

11.10Heart murmur, systolic Yes 1
No 2

11.11Heart murmur, diastolic Yes 1
No 2

11.12Carotid bruit. Left Yes 1
No 2

11.13Carotid bruit, right Yes 1
No 2

11.14Basal crepitations Yes 1
No 2

Appendix 13: Data cleaning

Data cleaning procedures undertaken (for both baseline and follow-up databases).

For the database containing the information from general practitioner notes:-

i) Checking for duplicates, including whether or not the same patient had been entered more than once, and whether more than one control had been identified for a given case and vice versa.

ii) Checking that date of birth for all patients corresponded to the inclusion criterion that they should be aged 60 years or over, and that the date of birth was appropriate (for example not born in 1828).

iii) Checking that a typically male/female forename corresponded to the sex assigned to the patient.

iv) Checking that cases had a control, that controls had a case and that controls did not have a control.

v) Checking that the date of echocardiogram was appropriate.

vi) Checking that the data of diagnosis of atrial fibrillation was appropriate and corresponded to the criterion of diagnosis of AF within the last five years.

vii) Checking that all cases had the section 'source of identification' completed. For those where this was not complete, the remainder of their record was checked to verify that they were true cases.

viii) Checking that those who had ever taken aspirin had an appropriate dose of aspirin recorded, and that all of those for whom a dose of aspirin was recorded had the box 'has ever taken aspirin' completed.

ix) Checking that the duration of time taking aspirin and warfarin was sensible, where this was completed.

x) Checking that those who had the section 'contra-indications to aspirin' or 'contraindications to warfarin' completed had the section 'has ever taken aspirin / warfarin' completed.

xi) Checking that those for whom contraindications to warfarin were listed had the answer 'yes' to the question 'are there contraindications to aspirin', and the same process for warfarin. Also check that those who had 'yes' to the question 'are there contraindications to aspirin' had contraindications listed, and the same process for warfarin.

xii) Check that those who were on warfarin had a record of the date warfarin treatment commenced.

For the database containing the information from the patient interviews and examinations:

i) Consistency checks were made with a proportion of interview and examination forms, against the data already entered onto the database, to ensure that there were no repeated sections of missing or inaccurate data. This process was applied to both baseline and follow-up interviews.

ii) The patient categories of 'control', 'case on aspirin', 'case on warfarin', 'case on neither', which had been based upon the data from GP notes, were compared with the actual prescriptions and replies to questions about warfarin and aspirin noted at interview, to ensure that all patients had been categorised appropriately. In addition the numbers in total and in each category were compared.

iii) Checking for duplicates (names and study ID numbers).

iv) Checking that date of birth for all patients corresponded to the inclusion criterion that they should be aged 60 years or over, and that the date of birth was sensible.

v) Checking that a typically male/female forename corresponded to the sex assigned to the patient.

vi) Checking the distribution of cognitive function test scores to identify outlying values which may be errors.

vii) Checking the clinical findings of 'regular' or 'irregular' heart rate on examination and atrial fibrillation or sinus rhythm on ECG against 'case' or 'control' status.

viii) Checking that cognitive function test results were sensible (e.g. time taken for an individual component was reasonable). Checking that all values were below the maximum score or above the minimum where maximum/minimum scores existed (e.g. maximum MMSE , minimum MMSE, maximum telephone task 1 and 3 score, maximum logical memory immediate and delayed, maximum Rey figure immediate and delayed, maximum map search test, maximum PASAT 2-second and 4-second, maximum NART, maximum digit-span).

ix) Checking the distribution of some variables such as blood test results, to identify whether or not these are near-normal, and to identify outliers which may represent errors in recording /data-entry.

x) Checking that no patients were taking both aspirin and warfarin at interview.

xi) Comparison of the patient information from GP notes with the information from interviews was made to identify missing patients.

xii) Checking of the whole database for missing data was made at regular intervals.

Any identifiable reasons for such missing data was documented, and where possible missing data was sought and the database amended. Examples of missing data that was identified include blood tests, which were for the most part missing due to patient's decline to have test, and family history.

xiii) Examples of checks run on this databases: cases were sorted in ascending order of NART number of errors, and this column was inserted next to the NART score column. Two observers then scrolled down the two columns and it was easy to identify any pairs which did not match (since there was often 5 or 6 of each pairing, it was easy to see where pairings did not match).

Appendix 14: Table of characteristics of CAFÉ individual general practices

Practice ID number	List size	Number of full-time partners	Number of part-time partners	Number of practice nurses	Method of anticoagulant monitoring	Level of Computerisation of records
1	5500	2	1	1	Secondary care	Partial - medication
2	7500	3	0	1	Secondary care	Partial - medication
3	6400	3	1	2	Secondary care	Almost fully – medication and most consultations
4	8600	5	0	2	Shared care (GP and secondary care) with plans for pharmacist-led clinics	Fully- paperless
5	13563	6	0	1.5	Pharmacist-led	Partial - medication
6	9700	4	0	2	Mostly secondary care	Partial - medication
7	3600	2	0	1	Some patients in primary care, some in secondary care	Partial - medication
8	5000	2	0	1	Pharmacist-led clinic	Partial - medication
9	14500	7	0	2	Some patients have GP/ district nurse, some secondary care/ district nurse	Partial - medication
10	9316	4	0	2	Secondary care	Partial - medication
11	5100	2	1	2	Pharmacist-led	Partial - medication

Practice ID number	List size	Number of full-time partners	Number of part-time partners	Number of practice nurses	Method of anticoagulant monitoring	Level of Computerisation of records
12	n/a	n/a	n/a	n/a	n/a	Partially – medication and some notes
13	2400	1	0	1	Secondary care	Partial – medication and disease registers
14	6500	1	3	2	PCG's pharmacist-led clinic	Partial - medication
15	7500	4	0	2	Secondary care	Partial – medication and disease registers
16	10024	3	0	2	Secondary care	Partial - medication
17	6238	3	1	1	Some patients in primary care, some in secondary care	Partial - medication
18	5900	3	0	1	Secondary care	Partial – medication, health checks, some medical history
19	4000	1	1	2	Secondary care	Partial - medication
20	12300	5	0	2	Some patients in primary care, some in secondary care	Partial - medication
21	4500	2	0	1	Some patients in primary care, most in secondary care	Partial - medication
22	6200	3	0	1	Pharmacist-led clinics	Partial – medication
23	4700	2	0	1	Secondary care	Almost fully – medication and some consultations
24	9100	4	1	1	Pharmacist-led clinics in	Fully

Practice ID number	List size	Number of full-time partners	Number of part-time partners	Number of practice nurses	Method of anticoagulant monitoring	Level of Computerisation of records
					secondary care	
25	2200	1	0	1	Some patients in primary care, some in secondary care	Partial – medication
26	1800	1	0	1	Secondary care	None – only admin
27	3100	1	0	1	Pharmacist-led clinic in primary care	Partial – medication
28	1700	1	0	0.5	Some patients in primary care, some in secondary care	Partial – medication
29	6681	3	0	1	Primary care	Partial - medication
30	6,500	3	2	1	Pharmacist – led (secondary care)	Almost fully – medication and most consultations
31	6,500	3	2	1	Pharmacist – led	Almost fully – medication and most consultations
32	6,500	3	1	2	Some secondary care, some GP	Partial
33	9,800	3	1	1	Secondary care	Partial
34	11,400	6	1	-	Secondary care	Partial – medication
35	3533	2	0	1	Secondary care	Partial – medication and consultation headings
36	3800	1	1	1	Primary care	Almost fully – medication and consultations
37	4000	2	0	1	Primary care	Almost fully – medication and some

Practice ID number	List size	Number of full-time partners	Number of part-time partners	Number of practice nurses	Method of anticoagulant monitoring	Level of Computerisation of records
						consultations
38	12500	5	1	2.5	Secondary care	Partial – medication
39	2800	1	0	1	Pharmacist-led	Partial – medication and patient summaries
40	n/a	n/a	n/a	n/a	n/a	n/a
41	n/a	n/a	n/a	n/a	n/a	n/a
42	n/a	n/a	n/a	n/a	n/a	n/a
43	n/a	n/a	n/a	n/a	n/a	n/a
44	n/a	n/a	n/a	n/a	n/a	n/a

Abbreviations:

GP = General practitioner

N/A= information not available

PCG = Primary Care Group (at time of recruitment – now Primary Care Trust)

Appendix 15: List of conference presentations and publications

I) Publications

Full Publications

- Park HL*, O'Connell JE, Thomson RG. **A Systematic Review of Cognitive Decline in the General Elderly Population.** *International Journal of Geriatric Psychiatry 18(12):1121-34, 2003*

Letters

- Park HL*. Gray CS. O'Connell JE. Thomson RG. In re atrial fibrillation. [letter; comment.]. ***Journal of the American Geriatrics Society***. 49(1):99-100, 2001 Jan.

II) Abstracts and Conferences

International

- Park HL*, O'Connell JE, Hildreth AJ, Thomson RG. Cognitive decline in the 'normal' elderly population – a systematic review. ***Abstracts from the Second International Congress on Vascular Dementia.*** Salzburg, January 2002. (Poster presentation)

- O'Connell JE*, Park HL, Hildreth AJ, Gray CS, Thomson RG. Silent cerebral infarction and cognitive impairment in atrial fibrillation. ***Abstract from the Fourth World Stroke Congress.*** Melbourne 2000. (Poster presentation)

UK

- Park HL*, Gray CS, Hildreth AJ, Thomson RG, O'Connell JE. Does atrial fibrillation cause cognitive decline? Follow-up results of the Cognition in Atrial Fibrillation Evaluation (CAFÉ). ***British Geriatrics Society Autumn Meeting***. London 2003. (Oral presentation)
  Abstract published in ***Age and Ageing*** supplement (in press).
  Note: won the E.Woodford Williams Prize for best oral presentation 2003.

- Park HL, Farrell AM, Gray CS, Hildreth AJ, Thomson RG, O'Connell JE. Cognition in atrial fibrillation evaluation (CAFÉ) – baseline results. ***British Geriatrics Society Autumn Meeting***. London 2002. (Poster presentation).
  Abstract published in ***Age and Ageing*** 2003; **32**: S13

- Park HL*, Gray CS, Hildreth AJ, Thomson RG, O'Connell JE. Is atrial fibrillation associated with cognitive decline? ***Northern Primary Care Research Network Annual Presentation Day 2003.*** (Oral Presentation)

- Park HL, Hildreth AJ, O'Connell JE, Thomson RG. An exploration of the rate of cognitive decline in the general elderly population through systematic review. ***46th Annual Scientific Meeting of the Society for Social Medicine.*** Liverpool 2002. (Poster presentation).

- Park HL*, O'Connell JE, Hildreth AJ, Thomson RG. A systematic review of cognitive decline in older people. ***British Geriatrics Society Spring Meeting.*** Telford 2002. (Poster presentation).
  Abstract published in ***Age and Ageing*** 2002; **31**:S(2)37.

- Park HL, Hildreth AJ, O'Connell JE, Thomson RG. An exploration of the rate of cognitive decline in the general elderly population through systematic review. ***46th Annual Scientific Meeting of the Society for Social Medicine.*** Liverpool 2002.

- Park HL*, Gray CS, O'Connell JE, Thomson RG. Cognition in atrial fibrillation evaluation (CAFÉ study). ***School of Clinical Medical Sciences Annual Research Presentation Day 2002.*** (Oral Presentation)

- Park HL*, Farrell AM, Gray CS, Hildreth AJ, O'Connell JE, Thomson RG. Cognition in Patients with Atrial Fibrillation – A Case Control Study. ***Annual Scientific Meeting of the Faculty of Public Health Medicine.*** Southport 2002. (Poster presentation)

- Park HL*, Hildreth AJ, O'Connell JE, Thomson RG. A Systematic Review of Cognitive Decline in Older People. ***Annual Scientific Meeting of the Faculty of Public Health Medicine.*** Southport 2002. (Poster presentation)

- Park HL*, Gray CS, O'Connell JE, Thomson RG. CAFÉ – Cognition and Atrial Fibrillation: An Ongoing Study. ***Northern Primary Care Research Network Annual Presentation Day 2000.*** (Oral Presentation)

Submitted papers

- Park HL, Hildreth AJ, Thomson RG, O'Connell JE. Non-valvular atrial fibrillation and cognitive impairment – baseline results of a longitudinal cohort study. Submitted to Journal of the American Geriatrics Society.

Papers in preparation:

- Park HL, Farrell A, Gray CS, Hildreth AJ, Thomson RG, O'Connell JE. Non-valvular atrial fibrillation and cognitive decline – follow-up results of a longitudinal cohort study. Target journal is *Stroke.*

Forthcoming conferences (abstracts accepted)

- Park HL*, Gray CS, Hildreth AJ, O'Connell JE, Thomson RG. Cognitive decline – is atrial fibrillation a risk factor? ***Annual Scientific Meeting of the Faculty of Public Health Medicine.*** Edinburgh 2004 (Oral presentation)

- Park HL, Hildreth AJ, Gray CS, Thomson RG, O'Connell JE. Is there an association between atrial fibrillation and cognitive decline? ***European Stroke Conference*** Mannheim 2004 (Poster presentation)

- Park HL, Hildreth AJ, Gray CS, Thomson RG, O'Connell JE. Atrial fibrillation and cognitive decline - is there an association? 12-month follow-up results of the cognition and atrial fibrillation evaluation (CAFÉ) ***5thWorld Stroke Congress*** Vancouver 2004 (Poster presentation)